ASTHMA AND THE ALLERGIC SYNDROME.

THESIS submitted for the

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by

CLARENCE ALEXANDER CALDER.

M.B.Ch.B. Edinburgh, 1920.
D.T.M. & H. England, 1923.

Physician - Maidenhead Hospital.

Physician - Ray Mead Childrens' Hospital.

Police Surgeon - Maidenhead.

Medical Officer - Jamaican Medical Service, 1921 to 1923.

Medical Officer - West African Medical Staff, 1923 to 1925.

Resident Medical Officer - Victoria Hospital, Dover, 1925 to 1926.

House Surgeon - West London Hospital, 1926.

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ASTHMA and the ALLERGIC SYNDROME.

INTRODUCTION.

The term "asthma" is derived from the Greek work ἄσθμα meaning "panting". It is used to denote a type of paroxysmal dyspnoea, produced by a spasmodic constriction of the bronchial muscle. It is necessary to realise that the condition is not just Bronchospasm. The latter may be produced in any individual by direct action, as by the action of local irritants such as sulphur dioxide or poison gas, or reflexly through the vagus from irritation in other parts of the body. The asthmatic syndrome, on the other hand, has certain definite characteristics.

1. It is paroxysmal and often nocturnal.
2. It is principally expiratory.
3. It has a definite hereditary element.
4. It often occurs in members of families where other diseases of similar causation occur - hay fever, urticaria.
5. It is frequently predisposed to by some psychic, nasal, toxic, endocrine or dietary factor.
6. It is accompanied by an eosinophilia in the blood.
7. It is relieved by an injection of adrenalin.

So the term merely expresses a symptom-complex.

It is no more a diagnosis than is dropsy or jaundice. It has been loosely used to describe this condition of the lungs wherein bronchial muscle spasm is associated with a certain amount of mucous membrane turgescence.

The protean manifestations of the syndrome have been for hundreds of years a source of much curiosity. The persistence of this curiosity through many generations has led to the elucidation of many of the problems. Gradually there has emerged the conception of a group of diseases, termed by Freeman the toxic idiopathies, due to a sensitization to particular proteins.

This group includes Asthma, Hay Fever, Angioneurotic Oedema, Intermittent Hydrarthrosis, some forms of Eczema and Gastro-intestinal disturbance. Some aurthorities would even include Prurigo, Dermatitis Herpetiformis, Migraine, Cyclical vomiting and some forms of Epilepsy.

It is important to bear in mind the existence of these allied conditions and to regard Asthma as a symptom or mode of reaction to various irritants which in this instance give rise to manifestations in the bronchial tree.

The whole subject appears to centre around the word Hypersensitiveness. This includes all

reactions in which hypersusceptibility to some foreign agent is evidenced as compared with normals. It may be divided into (1) Anaphylaxis and (2) Allergy. The former is the term applied to the induced manifestations of hypersensitiveness in laboratory animals, and is due to an antibody-antigen reaction occurring in special sensitised tissues. Allergy is the term applied to:-

(a) natural or spontaneous manifestations of hypersensitiveness in man,

Asthma, hay fever, eczema, urticaria, and migraine,

and to

(b) induced states such as serum sickness and the passive transfer of hypersensitiveness by sensitized serum.

Allergy is thus a state of exaggerated susceptibility to various foreign substances or physical agents that are harmless to the great majority of ordinary normal individuals. As Von Pirquet truly said, it is a state of altered reactivity.

There are thus some points of dissimilarity between Anaphylaxis and Allergy. The following table outlines the main points:-

Anaphylaxis.	Allergy.
All of the suspected species of animal can be rendered anaphylactic.	Only a small percentage of human beings are Allergic (1 to 2 per cent)
Transmission is usually acquired.	Transmission is frequently inherited.
A sensitizing dose is required.	A sensitizing dose is not always necessary.
A provocative dose is necessary after ten days.	A time interval is unnecessary.

Any substance capable of producing an antibody is known as an antigen. Anaphylaxis is an antigen-antibody reaction. The allergic exciting agent is called the allergen, and the allergic antibody is the allergin. Cells are sensitised when the allergin is in or on them and thus accounting for their altered reactivity. When the allergen comes in contact with the allergin in these sensitized cells a rapid reaction occurs, resulting in the production of the lesions and symptoms of allergy. If there be enough allergin circulating in the blood to neutralise all the allergen and so prevent its access to the sensitised cells, it may prevent an allergic reaction. This allergic response may

occur after the inhalation, ingestion, injection or skin contact with the substance in question. Some specific sensitising substance does certainly circulate in the blood of allergic individuals, as shown by the Prausnitz-Kustner reaction. This substance is not identical with precipitin, for the latter is unnecessary in the mechanism of Allergy. A definite familial tendency to develop hypersensitiveness of some kind is present. The source of antigen includes plants, animal emanations, sera, environmental dusts, foods, vapours and smokes, insects, bacteria and physical agents. According to Kolner (1928) Antigen should be divided into:-

(a) proteins or closely related substances, and

(b) substances of an unknown chemical nature.

The allergic antigen in many instances is, in itself, not protein in nature - e.g. drugs, bacterial products and specific plant oils. It has recently been shown by Avery and his co-workers (1917-1929) that the peculiar biphasic reaction often present in bacterial allergy is due to the chemical structure of the allergen and especially to the carbohydrate radical.

The human body responds to the presence within

it of allergens by certain definite reactions. Most of the experimental work done on anaphylaxis and allergy has followed two definite lines,

1. Experiments dealing with the musculature and innervation of the lungs and bronchi in man and animals, and
2. Experiments dealing with the formation of histamine or histamine-like substances and the resultant circulatory and smooth muscle responses.

In 1903, there were four current views as to the etiology of asthma:-

(a) Spasm of the Bronchial muscles. First suggested by Cullen (1788). Supported by Laennec (1835), Voltmann (1844) and Einthoven (1892).

(b) Swelling of the Bronchial Mucous Membrane. First proposed by Parry (1844) and then upheld by Biermer (1854) and Clark (1886).

(c) Special form of Bronchiolitis. First suggested by Traube (1847). Later upheld by Curschmann (1882).

(d) Reflex spasm of the Inspiratory muscles. First proposed by Budd (1839) and later upheld by Wintrich, Riegel and Edinger (1882).

Since 1903, Brodie and Dixon and other workers,

faced with these four conflicting opinions, have been endeavouring to settle on one particular view. They decided that most support should be given to the bronchial muscle spasm and reflex theories.

Histamine has been shown to be present in most of the body tissues. It is formed from histidine, which is a component of every known protein. When histamine is injected intravenously into animals it produces:-

1. shock, characterised by marked smooth muscle contraction, and
2. a marked fall of blood pressure, due to dilatation of all the peripheral blood vessels.

And when histamine is applied to the skin of animals or man it produces prompt wheal formation, such as is seen in allergic persons when the specific allergen to which they are sensitive is applied to the skin. Because of these two phenomena and because it is so prevalent in the tissues of the body, as well as capable of being produced in the lumen of the intestine and lungs, histamine is now attracting a great deal of attention.

Now, it appears that all are agreed that the lung manifestations of hypersensitiveness are

brought about by bronchial muscle spasm. Though the earlier investigations emphasized the importance of stimuli passing along the vagus from reflex causes, or from an irritable bronchial centre or bronchomotor portion of the vagus, later observations would emphasize the chemical and bio-chemical aspects. It would seem possible that the vagus may be made more irritable than normal by the circulation of foreign protein. Foreign protein can easily get into the blood (vide Prausnitz-Kustner reaction), but it may be that the irritability of the vagus is produced only when large quantities of incompletely digested protein enter the circulation.

So fundamentally, there is a marked similarity between asthma and the phenomenon of Allergy. Indeed, asthma appears to represent the lung manifestations of allergy. All allergic diseases have very marked characteristics. These are as follows:-

1. periodic symptoms, frequently worse, or having their onset at night;
2. history of other allergy in the patient's previous or present history.
3. history of allergy in other relatives or offspring;

4. ability of the akin or mucous membrane to react positively to specific allergens when applied;
5. blood eosinophilia;
6. hypochlorhydria on fractional gastric analysis;
7. response to adrenaline.

Each characteristic in turn applies equally to asthma. Forty years ago asthma was grouped with paroxysmal neuroses, such as migraine and epilepsy. This conception has been rather driven into the background by the explanation that it is an allergic phenomenon, resembling but not identical with anaphylaxis. Wacker and Rachemann of Boston, Freeman and others have shown this conclusively, and yet all cases cannot be brought under this heading. Hurst enlarges on this conception of asthma as an allergic phenomenon. He regards it as the reaction of the over-excitable bronchomotor portion of the vagus nucleus to blood-borne irritants and to peripheral and psychical stimuli. Vagal irritation has been postulated as the cause of asthmatic attacks by many observers, notably by Eppinger and Hess (1909). They showed by experiments with pilocarpine and adrenaline that many clinical.

conditions arose from dysbalance of the sympathetic and parasympathetic elements of the vegetative nervous system. Since the classical example of vagal stimulation in man is bronchospasm, asthmatics should be classified as vagotonics. Asthmatic spasms should be then aborted by the administration of atropine, but such an immediate effect is rare. Langdon Brown supported the theory of Eppinger and Hess that the asthmatic patient is a vagotonic. It is claimed in support of this that hypodermic adrenalin acts dramatically in relieving the asthmatic paroxysm, as if to prove the presence of excessive parasympathetic activity. On the other hand, morphine injections and amyl nitrite inhalations will also relieve attacks. Moreover, the subject of Addison's disease is not specially prone to asthma, although there is marked adrenal insufficiency present. In fact, relative vagotonia does not appear to be important in the causation of asthma. It is certainly far more attractive to consider that in asthmatic and allied conditions there are two etiological factors:-

1. The exciting cause, a foreign protein, or a mechanical or psychical stimulus, and
2. the predisposition - the presence of vagotonia or hypersensitiveness.

Moreover, each subject must present these two factors for the allergic phenomena to occur. Psychological factors can only produce asthmatic attacks in an asthmatic - in other words, the allergic basis must be present before psychic traumata can produce a reaction. The altered reactions of allergy are not confined to abnormal reactibility of nonstriated muscles or secretory organs, but they occur rather frequently in other tissues, such as the central nervous system, and cause the patient to react in exaggerated ways to certain specific material impressions and sensations. The question arises whether in asthma and allied conditions there is some underlying factor - vagotonia - which predisposes the subjects to become hypersensitive to foreign proteins and other stimuli, or whether hypersensitiveness is the only factor, in some instances at least.

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HISTORICAL

It is very interesting to trace the development of our knowledge of this particular subject. It is, moreover, quite remarkable to observe the alacrity with which the various points have been seized upon and elaborated throughout this history. It is possible to recognise two distinct periods in the development of our knowledge of asthma. The first period was one of clinical observation and really began in 1698 with Sir John Floyer's treatise, and ended with the Great War. The second, beginning about 1920, has been the period of intensive laboratory investigations, combined with the older clinical methods.

Caelius Aurelianus (fifth century A.D.) was the first to give a just and accurate account of the asthmatic spasm. From this time until the year 1650 very little new knowledge appears to have been gained. Then the whole subject gradually began to flare up. The first factor to be established was the Hereditary one. In 1650, Sennertus described how his wife's father, two brothers, a sister and a sister's daughter, all laboured under the complaint. Sir John Floyer (1698) stated, "As my asthma was not hereditary from my ancestors, so, I thank, God, neither of my two sons are inclined to it, who

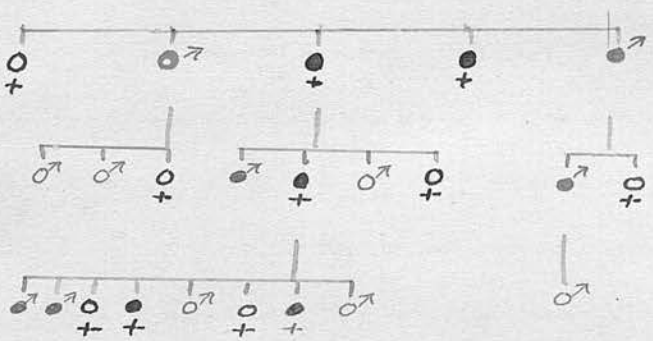
are now past the age in which it seized me."

Cullen (1784), Ryan (1793) and Davidson (1795), all suggested its hereditary transmission. This was also the generally accepted opinion in America, according to Eberle(1831). Salter (1860-1868) found distinct traces of inheritance in 84 of 217 cases. In 1909 Drinkwater recorded a very impressive pedigree. See Page 14.

And so to this day, statistical surveys show that the majority of allergic individuals have one or more antecedents with some type of allergic manifestation. In nearly 70 per cent. of cases of asthma, it will be found on careful history-taking that there is a positive family history of allergy.

It is perhaps as well to regard Jenner's observation (1798) about the inoculation of smallpox as the first definite reference in the history of Allergy and Anaphylaxis. In 1839, Magendie found that dogs died suddenly if they had been injected repeatedly with egg albumen. Then Flexner (1894) found that animals that had withstood one dose of dog serum succumbed to a second dose given after a lapse of some days or weeks, even if sublethal for a control animal. It was left, however, to Richet (1902) to recognise why

DRINKWATER'S PEDIGREE (1909)



Completely shaded circles — ●● = asthmatic patients

this should occur. He pointed out that the hypersusceptible condition depended upon a preceding inoculation with the same substance, and that before such susceptibility develops there must of necessity be a definite incubation time. This phenomenon he named "anaphylaxis", as opposed to prophylaxis. For his experiments, he used eel serum and a glycerin extract of the tentacles of the sea anemone.

In 1904, Theobald Smith, whilst standardising antitoxin, noted the development of this anaphylaxis in his guinea-pigs, and pointed it out to Ehrlich. Otto (1905) showed that the phenomenon was quite independent of the toxin and antitoxin it contained and could just as easily be produced by using horse serum alone. About this time also, it was hinted for the first time that human hypersensitiveness was related to anaphylaxis as observed in animals. Weichhardt and Wolff-Eisner (1905) suggested this when discussing hay-fever. Among those interested in the subject was Von Pirquet. He set about investigating serum disease, and, as a result of his investigations, came to the conclusion that an antigen - antibody reaction was its basis in general. He thereupon coined the term "allergy"

or "allergic", meaning altered reactivity. The study of anaphylaxis was carried a good bit further by Rosenau and Anderson (1906-8). Diphtheria antitoxin, powerful remedy as it was, happened to be in disfavour because of the occasional sudden deaths during its use, and they were investigating as to the cause of these deaths. They found that a slight injection of horse-serum into guinea-pigs, harmless in itself, rendered them hypersusceptible to subsequent injections given after an interval of ten days, that this reaction was specific and extremely delicate, and that the sensitive condition was transmissible from mother to offspring. They also discovered that the hypersusceptible state may last a long time, and, more important, be brought about by various animal and vegetable products and bacteria. Four years later, Auer and Lewis made a detailed study of the mechanism of anaphylactic death. The bronchial constriction observed in animals so dead led Meltzer (1910) to suggest that true bronchial asthma was an anaphylactic phenomenon, the bronchial constriction in asthma being so very similar.

Koessler made similar observations

about the same time, and in 1913 he reported a case of asthma due to hypersusceptibility to hen's eggs. Doerr (1912) extended the use of the word Allergy to embrace reactions due to bodies other than antigens. The etiology of anaphylactic shock has been a subject of much investigation during this century, and many theories have been advanced - toxic (Richet), physical (Doerr and Bordet), organic (Besredka and Weil), proteolytic (Vaughan and Herb) and histamine (Barger and Dale). In 1910 the latter two isolated histamine as an active factor from ergot and later from the gut. They demonstrated its toxic properties and further showed that it is present in most of the tissues of the body. Dale and Laidlaw (1910) showed that the injection of it into guinea-pigs produced symptoms similar to those observed in anaphylaxis. Lewis (1921-1927) concluded that the response of the skin to injury or stimuli is intimately concerned with the release of a substance, which is either histamine or has a histamine-like action. More recent work carried out by Dale (1929) suggests that the local liberation of a substance with a histamine-like action may be one factor in the chain of events leading up to the final production

of the anaphylactic response. Next year (1930) Knott and Oriel detected histamine-like substances in asthmatic and other sputa. They suggest that these substances are formed from the growth of bacilli within the small bronchial tubes, and that they form one cause of locally produced asthma.

The next important step was the observation of Jenner (1798) - an observation which was to become the forerunner of the present-day practice of skin testing - namely:-

the sudden appearance of an "efflorescence of a palish red colour" about the parts where variolus matter had been applied to the skin of a woman who had had cow-pox thirty-one years previously. Then was to follow in 1868 Hyde Salter's classical description of cat asthma - a phenomenon which he believed almost peculiar to himself. Any part of the body surface was equally affected by a claw puncture. Around the actual puncture was a hard white elevation or wheal accompanied by pain, irritation and itching. Fingers that had handled a cat affected the eyes and lips when touched; in the former was a hot, stinging, irritation, a profuse flow of tears, a tender painful swelling of the caruncle, and injection

of the whole eye and intolerance of light; the lips became swollen at the point touched, together with a feeling of heat and irritation. Five years later, Brackley showed that crude pollen produced similar phenomena in hay-fever patients. Dunbar and Arthurs (1903) carried these investigations a bit further; and in 1905, Von Pirquet and Schick made a valuable observation. They were, at the time, engaged in studying serum disease. They found that the re-injection of horse serum caused an intensive oedema around the point of injection if a period longer than seven to ten days had elapsed since the first injection. Von Pirquet, two years later, claimed that his tuberculin reaction was of the same nature. From then on, observers began to use skin reactions in clinical allergy. First, Moss (1910) advocated that dangerous anaphylactic symptoms could be avoided by their use in advance to determine susceptible cases. Noon and Freeman (1911) in this country, and Cooke (1911) in America, the former using the conjunctival route and the latter the intradermal, then demonstrated the practical uses of these tests in diagnosis, and initiated the practice of desensitisation by prophylactic inoculation of gradually increasing.

doses of the causative pollen, as determined by the tests. Schloss (1912), Goodall (1914) and Talbot (1914) further elaborated these ideas. Today, protein skin reactions, carried out with proper technique, occupy one of the very most important positions in our diagnostic armamentarium.

Within recent years much work has been done in the identification of the specific protein to which given individuals are susceptible. This is a very great advance, for, by eliminating the susceptible elements from the diet, environments and so on, allergic individuals can be kept free from their distressing symptoms in nearly all cases. Particularly is this the case with children. Peskin (New York) has shown that 49 per cent of asthmatic Jewish children gave positive reactions to rabbit hair on which they slept. Balycat (Oklahoma) found 43 per cent sensitive to feathers, which comprised their bedding. Bray (London) similarly has shown that two out of every three asthmatic children will give a positive reaction to feathers or horsehair or both. In children, it has been found most successful to test first for environmental factors. In infants, on the other hand, food reactions are best performed first.

Obviously, a very detailed history is most important. Bacterial sensitiveness does not appear to play an important role in the allergic reactions of infants and children. So that skin reactions have their greatest sphere of usefulness in the testing of children and young adults, and in patients sensitive to pollens and other air-borne allergens. The methods of finding out the particular allergen are now definite. First, the substances used are divided into four classes:-

1. Inhalants. - (a) Animal emanations.
   (b) Dusts.
   (c) Pollens.
   (d) Moulds and fungi.

2. Ingestants. - (a) Milk.
   (b) Eggs.
   (c) Cereals and so on.
   (d) Yeasts.
   (e) Drinks such as tea.

3. Infectants. - (a) Bacteria (autogenous for preference).
   (b) Helminths.

4. Injectants. - (a) Sera.
   (b) Drugs.
   (c) Bites.
   (d) Stings.

These are all put up in the form of pastes, fluid extracts, tablets, dried powders and filter papers.

Secondly, the tests are performed either through the skin or through mucous membranes. In 1921, a very important reaction was discovered, called the Prausnitz-Kustner reaction. The

serum of Kustner, who was sensitive to fish was introduced into the skin of Prausnitz. Then it was found that by intradermal test, the skin of Prausnitz had become locally and passively sensitized to fish at the injected site. Obviously, this is of great value when the usual skin tests are not practicable.

The question of asthma being of nervous origin has been raised for over a century. As early as 1818, it was recognised that the etiology of asthma must be very varied. Rostam described two types - one in which the dyspnoea could be accounted for by the sufficiency of pathological changes, and the other in which there was no such pathology. The latter he named nervous asthma. In 1847 an interesting case of this so-called nervous asthma was described by Ramadge. He tells how a girl servant had a violent attack of asthma whenever she obtained a new situation with which she was pleased, in consequence of which she had to give it up. Salter (1868) and Trousseau (1882) both considered that asthma was nervous in origin. These were all astute enough to observe the manner of the attack. They, however, failed to grasp how this so-called nervousness acted. Bosworth (1886) was the first to recognise the

importance of the trio, a neurotic temperament a diseased condition of the nasal mucous membrane, and an air-borne exciting substance. Both Gauldrini (1906) and Gibson (1911) recognised the part played by emotion in instigating attacks. It was not, however, until Eppinger and Hess (1909) carried out their experiments with pilocarpine and adrenaline that such a possibility as a dysbalance between the sympathetic and parasympathetic systems was considered as in any way an explanation of this nervous element in asthma. Then in 1915, Berkart published a monograph, in which many ingenious theories as to the nervous origin were put forward. It was most difficult to associate these nervous theories with any allergic basis. In 1922, however, Shannon found that the allergic reactions to proteins, to which the patient has become sensitized, irritated the nervous system and gave rise to many of the symptoms of the neuropathic diathesis. This has been later upheld by Duke (1927). And in 1930, Vaughan recounted the case of a child in whom chronic food allergy quite changes the personality of the individual at times.

There is no doubt that phychology also plays a part in asthma. Langdon Brown (1922) and later McDowall (1930), both make a point of this in their formulae for asthma. It is well known that 75 per cent of patients become either completely or almost entirely free of symptoms directly they enter a hospital, no doubt due to the expectation of benefit to be derived. Indeed, Hurst (1929) considers expectation to be the most common psychological factor. Perhaps expectation would also account for the successes in treatment with hypnotism. Both Strauss (1927) and Kholy (1929) describe authentic cases in which persuasion and re-education proved very effective. Hansen (1929) showed that hypnotism will frequently cure a fully developed attack. Still more interesting is Francis' view (1929), that asthma is merely a symptom of vasomotor instability, for he describes how the touching of the nasal septum at certain points has led to relief in over a thousand cases, a fact which he discovered accidentally in 1896.

So it is obvious that mental and psychic states do provoke allergic responses. The

important point to note is that they do so only in those persons who are already allergic. A historical outline would be incomplete without reference to various other factors in this important syndrome. Foremost among these is the part played by nasal pathology. This was first recognised in 1844 by Herck. It was discovered that cases of asthma were cured by the removal of nasal polypi. In 1903, Brodie and Dixon produced bronchospasm by stimulation of the nasal mucosa in certain parts, which led to asthma being considered a nasal reflex. This gave rise to various surgical methods of treatment with very varying results.

In the last thirty years, various other factors have been incriminated, notably the endocrine and the toxic. Syphilis and tuberculosis have each had their turn.

In 1898, a very notable advance in our knowledge was made. Solis-Cohen, himself a sufferer from asthma, reported great improvement from the oral use of adrenalin. It was not, however, till 1910 that Melland urged its use in England. In the last two years, the alkaloid from a Chinese herb, Ma Huang, has been used with success, under the name of ephedrine.

Among the various other examples of allergy, there is one, the history of which dates back many years and is associated with many interesting events - that is pollen-allergy or hay-fever. As early as 1565, a case is quoted by Pavia of a woman in whom the odour of roses produced a headache, itchiness of the nose and sneezing. More dramatic is the story of a Roman Cardinal who had to have the palace gates kept constantly guarded lest anyone should enter carrying a rose, as recounted by Herlinus (1693). In 1819, the etiology of the subject was founded on a sure basis by Bostock's illuminating description. And during the rest of the nineteenth century, various observers elaborated his contentions, and the terms "hay-fever" and "summer catarrh" came into general use. Identification tests for the special pollens were the next step - this was carried out in 1911 by Noon and Freeman in England and Cooke in America, and it was soon followed by the therapeutic use of the pollens indicated. Desensitization was first really put on a scientific basis by Koessler (1914) in America.

Cutaneous allergy became an established

fact only about 15 years ago, as the result of work carried out along two separate line. Cooke and Vander Veer (1916) were able to show that eczema and urticaria occurred in members of families in which there was a strong history of asthma and hay-fever. The second work of inquiry, carried out by Schloss (1915), Blackfan (1916) and Strickler (1916) proved clinically that the eczema of infants and children was frequently due to food sensitization. Since then many observers have upheld these views. Due credit must, however, be given to Von Pirquet (1911) for first suggesting that urticaria was of an allergic nature. The pathology of the urticarial wheal has been investigated by Dale (1918) and Lewis (1927), who claim that the wheal is due to the liberation locally of some histamine-like substance.

French authors have for many years maintained that migraine should be classified with asthma and eczema. It was, however, not ascribed to an allergic basis until Strümpell spoke of it as an exudative process comparable to urticaria and angioneurotic oedema. Vaughan (1922) obtained positive skin reactions to foods in several instances.

Of recent years, various observers have been suggesting that muco-membranous colic is an allergic phenomenon. Hurst (1910) first outlined the similarity between this colonic spasm and asthma. And the contention has been further strengthened by the views of Bastedo (1917) and Vaughan (1922).

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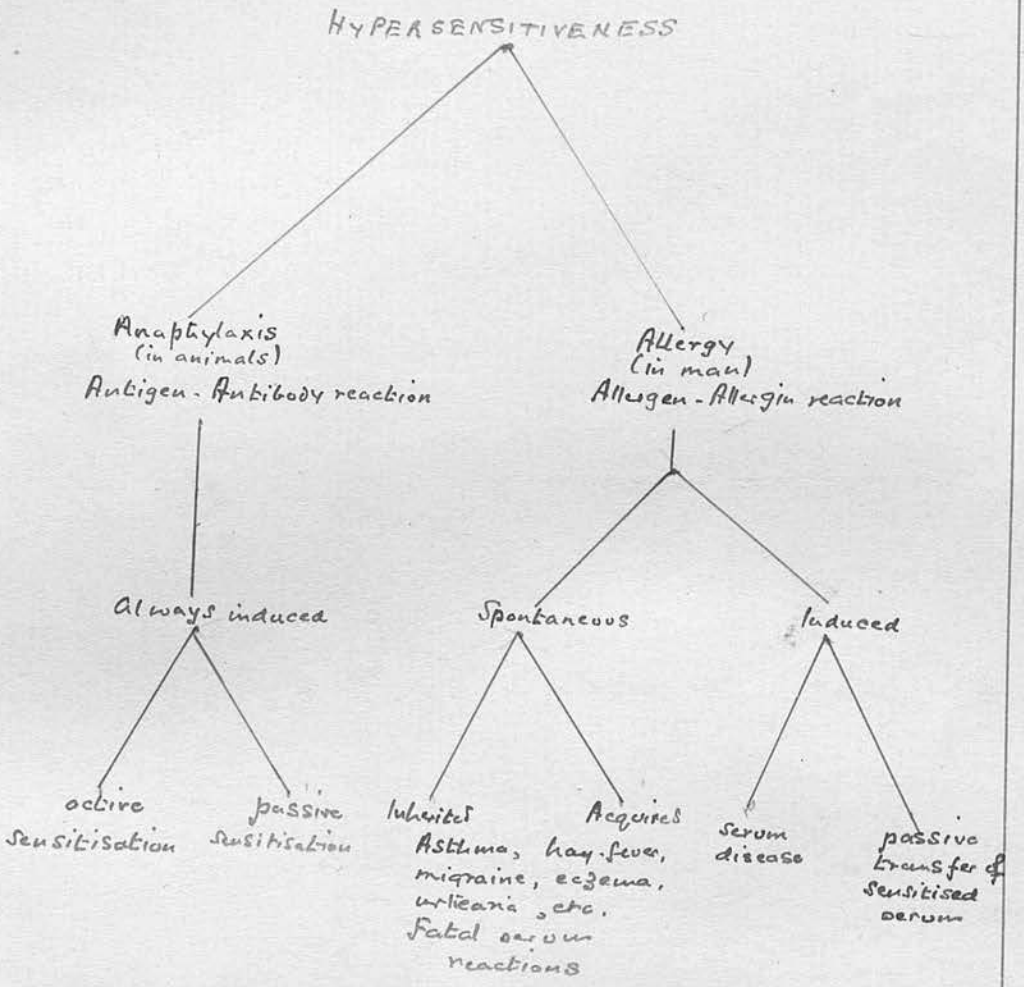
GENERAL ETIOLOGY OF ASTHMA AND KINDRED DISORDERS.

Relationship of Asthma to Anaphylaxis and protein sensitiveness.

This has, to a certain extent, been discussed in the Introduction. Recapitulation will serve to emphasize its importance. The diagram on page 30 (Bray)(1.) is exceedingly helpful in the study of the subject.


HYPERSENSITIVENESS
Anaphylaxis
(in animals)
Antigen - Antibody reaction
Allergy
(in man)
Allergen - Allergin reaction
Always induced
Spontaneous
Induced
active
Sensitisation
passive
Sensitisation
Inherited
Asthma, hay-fever,
migraine, eczema,
urticaria, etc.
Fatal serum
reactions
Acquired
Serum
disease
passive
transfer of
Sensitised
serum

With all attention turned towards the elucidation of the problems of asthma and every new item of interest being pounced on and thoroughly explored, Meltzer's (2) description of the similarities between the lungs of asthmatics and those of guinea-pigs dead of anaphylactic shock was received with great relief. So asthma and anaphylaxis must be the same after all, it was thought. Gradually, however, it has become evident that this so-called "anaphylaxis in man" violated many of the principles of anaphylaxis in laboratory animals. Now anaphylaxis is of two kinds - (a) active and (b) passive. In the former, one injection of horse serum renders an animal hypersusceptible to a subsequent injection given after a definite interval of about nine to fourteen days, a second injection after this time being generally fatal. The temperature falls, the blood pressure falls, the coagulability of the blood is lowered and there is a leucopenia. At autopsy, the chief pathological condition is a contraction of the smooth musculature of the bronchioles, resulting in an inflated condition of the lungs. Active anaphylaxis is brought about by antigen, Passive anaphylaxis by antibodies.

If an animal is sensitised and some of its blood injected into another animal, this second animal becomes passively sensitised, after fifteen to eighteen hours, to the substance which sensitised the original animal. A similar state can be produced in offspring by sensitising a pregnant female. So that any serum which contains antibodies can effect passive anaphylaxis; the power to do so is in direct proportion to the antibody concentration. The symptoms of anaphylaxis vary in different animals, perhaps due to the peculiar anatomical distribution of the non-striated musculature in the various species. Some species of animals are more susceptible than others, the guinea-pig being the most susceptible. The severity of the anaphylactic reaction also depends upon the mode of administration - severest reaction being produced when the intravenous route is used, and the mildest when the skin route is employed. The severity also depends upon, of course, the dose of antigen administered, as also upon the origin, strength and age. There are thus certain characteristics of anaphylaxis which it would be well to summarize:-

1. it denotes a state of sensitivity manifested on re-injection of antigenic substances into animals under given conditions;
2. of any susceptible species of animal, all the members can be rendered anaphylactic;
3. a sensitising dose is always required, and a provocative dose is necessary after ten days;
4. it is due to immune bodies - precipitins, anaphylactins;
5. first and repeated reactions can only be produced by a multiple of the sensitising dose;
6. it is produced by soluble protein substances;
7. (a) it is usually acquired;
   (b) if inherited, it is through the mother.
   (c) it is only against the same substance as the sensitised mother.
   (d) its duration in the young is short.
8. the reaction is always the same for a given species of animal, no matter what antigen is used;
9. the outstanding lesions vary according to species e.g. bronchial spasm in guinea pigs;
   liver changes in dogs;
   pulmonary arterial constriction in rabbits;

but most are due to contraction of non-striated muscle.

Now, in the historical section, it has been shown that for many years various observers had realised that certain persons respond in an abnormal manner to substances that are quite harmless to an ordinary individual. Von Pirquet (3) no doubt thought that anaphylaxis, as seen in animals, did not quite apply to this condition of hypersensitiveness in man. So he invented a new term - Allergy - meaning altered reactivity; but he held that the basis was an antigen-antibody reaction. This has now been modified to an allergen-allergin reaction, the explanation of which is described in the introductory section. Von Pirquet based his theory on inference and not on experimental observation. Anaphylaxis has not been demonstrated in man, although it is impossible to assert that it does not occur. On the other hand, allergy is exhibited conclusively in human beings. This hypersensitiveness in the latter may be manifest after the inhalation ingestion, injection or skin contact with the substance in question. In normal individuals, a small amount of unchanged protein is certainly absorbed, for this has been shown experimentally. So it cannot be thought that the absorption of

foreign native proteins through the various channels mentioned above could account for the sensitisation observed. This hypersensitive state in human beings is characterised, too, by certain essential features. These are:-

1. it represents peculiar reactions occurring after the use of foreign serum, tuberculin or vaccination;
2. that only a small percentage of human beings are allergic - one to two per cent;
3. it differs from anaphylaxis in that it is not always necessary to have a sensitising dose, nor is there need for any time interval;
4. it is due to allergens of unknown immunological nature;
5. first and repeated reactions can be elicited with identical infinitesimal quantities of the related allergen;
6. it is also produced by many non-protein substances;
7. (a) it is frequently inherited;
   (b) inheritance is through the father as well as the mother;
   (c) it is against various substances;
   (d) its duration in the young is long;
8. the reactions mainly take place in the skin, respiratory and gastro-intestinal tissues;

9. different tissues may vary so absolutely in their sensitiveness to the same protein that the impression is obtained that sensitivity is highly developed in some tissues and entirely absent in others;

If now the characteristics of anaphylaxis and allergy are compared, it is obvious that they are two definite conditions, the one occurring in laboratory animals and the other in human beings.

And yet this allergic theory does not appear to embody the whole question in these cases of altered reactivity to varied substances in human beings. There are other important modifying or predisposing factors, though these alone could not themselves wholly explain the phenomenon. All must be blended in; that is, there must be a balanced allergic state, as Vaughan (4) admirably suggests. The common constant factor is generally an inherited, occasionally an acquired, predisposition to manifest hypersensitiveness to specific allergens which are of an inhalant, ingested, infectant or injected nature. While these specific allergens are the exciting cause of any response or loss of equilibrium, there are many other non-

specific, non-allergenic causes that may act as predisposing factors to disturb this equilibrium. These mon-specific factors may be psychic, endocrine, toxic, nasal, dietary or environmental. Should such a factor be disturbing the balance when the specific allergen intervenes, then allergic symptoms will ensue. In the balanced state, however, these same allergens may not be sufficiently potent to upset the balance, except in rare cases of extreme susceptibility.

Again, to recapitulate, all allergic diseases have certain definite characteristics. These are:-

1. periodic symptoms, frequently worse or having their onset at night;
2. history of other allergy in the patient's previous or present history;
3. history of allergy in other relatives or offspring;
4. ability of the skin or mucous membranes to react positively to specific allergens when applied;
5. blood eosinophils;
6. hypochlorhydria on fractional gastric analysis;
7. response to adrenaline;

Asthma is related to anaphylaxis in so far as the lungs of guinea-pigs dead of anaphylactic shock present remarkable resemblances to those of asthmatics. In both conditions, there is a contraction of the non-striated muscle of the bronchi. The relation of Asthma to Allergy is pronounced. All the above quoted characteristics of allergic diseases are well-marked. Every non-specific factor concerned in allergy is known to be of paramount importance in asthma. In fact, it can be definitely stated that asthma is a spontaneous manifestation of allergy, a condition occurring in man which corresponds to that of anaphylaxis in laboratory animals, both merely expressing a state of hypersansitiveness to foreign proteins.

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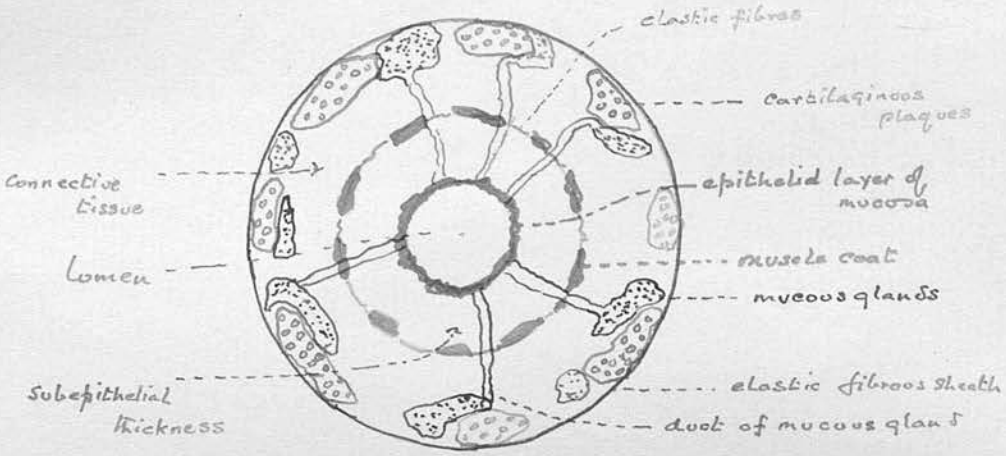
THE CAUSATION OF THE BRONCHIAL OBSTRUCTION

Up to 1903, there were four current views. These were:-

1. Spasm of the Bronchial muscles;
2. swelling of the Bronchial mucous membrane;
3. special form of Bronchiolitis or excessive bronchial secretion;
4. reflex spasm of the inspiratory muscles.

The structure and mechanics of the lung have a most important bearing on the asthmatic condition, so must be studied in some detail. The main bronchi divide into a series of bronchi and bronchioles, there being a strong supporting element of cartilage in the larger. Consequently, marked bronchial contraction can only occur in the smallest bronchi. At the point where the ring of cartilage ceases to be continuous and becomes divided into irregular elements around the bronchus, the epithelium also changes from a stratified ciliated columnar type to a squamous form, and mucous glands disappear. The muscular element of the bronchus, which is the most important so far as this subject is concerned, is of very great interest. The strands of muscle do not run straight down the lung axis of the bronchus but irregularly obliquely. And, as they

are traced down to the smallest bronchi, it is important to note that these muscle bands appear to get larger proportionately to the other constituents. Indeed, in the terminal bronchiole, they form quite a conspicuous structure, The muscle coat lies between the cartilaginous and mucous coats, so that when it contracts, the mucosa is thrown into folds. A diagram of a small bronchus in cross-section will serve to illustrate the anatomy.



CROSS. SECTION OF A SMALL BRONCHUS.

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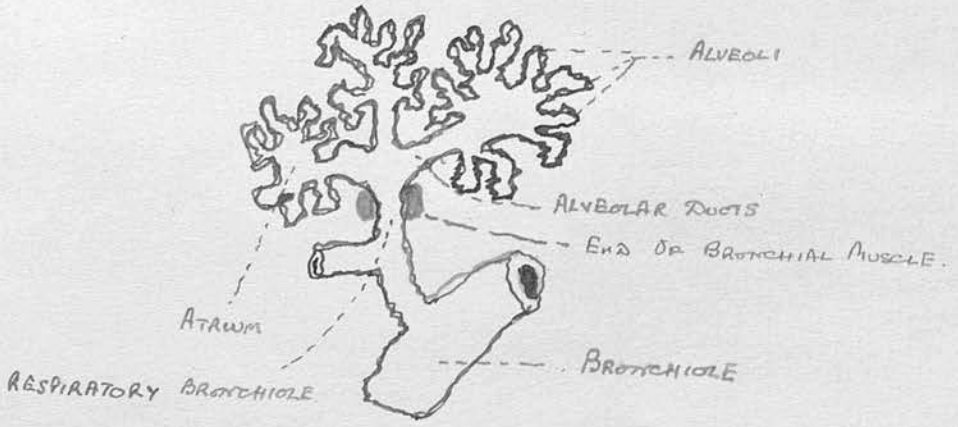

DIAGRAM SHEWING EXPANSILE PORTION OF LUNG WITH MUSCULAR BANDS ON TERMINAL BRONCHIOLES.

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As was pointed out, the musculature of the smallest bronchiole is relatively most strongly developed; and, of course, the lumen of the terminal bronchiole is the narrowest of the entire bronchial tree. Consequently, when its walls contract, its lumen may be completely obliterated. Now it is in this region that the site of reaction in allergic conditions lies. There being no muscular elements in the walls of the alveoli, these muscular bands more or less act as sphincters on the terminal bronchioles.

The bronchial musculature regulates the tension of the air in the alveoli. Another interesting point is that the terminal part of the alveoli - the infundibula - are conical and taper towards the bronchioles. So that if the bronchioles are constricted, air will enter owing to the negative pressure caused by the inspiratory movements of the thorax and diaphragm, but it becomes exceedingly difficult for expiration to occur, as the slender walls of the alveoli have to bear the brunt of expiratory pressure. Consequently, the lungs become over-distended.

In 1903, Brodie and Dixon (5) set out to try and settle this question of the causation of the broncial obstruction. It was known that

the vagus was the motor nerve to the bronchial muscle and that stimulation of it caused bronchial obstruction. It was also known that the rami of the first, second and third thoracic nerves, as well as the cervical sympathetic, contained broncho-dilator fibres. If a stimulus was applied to the nasal mucous membrane, the cornea, or the divided vagus, reflex bronchial constriction resulted, but not when the stomach or intestine or a cutaneous sensory nerve were stimulated. Brodie and Dixon were able to show experimentally that certain drugs caused broncho-constriction and others broncho-dilatation. Among the former were pilocarpine, carbon dioxide and morphine and lobelia very slightly; among the latter were atropine, chloroform and ether, and lobelia and morphine, following their slight constricting effect. These two observers thereupon strongly supported the bronchial muscle spasm theory, because:-

1. it was induced by pilocarpine and immediately relieved by atropine or sympathetic stimulation, experimentally;
2. of the nature of the attack, clinically, with its rapid onset and abrupt termination, and
3. antispasmodic drugs relieved the condition empirically;

Now, the bronchiolar mucous membrane is very thin and has a relatively poor blood supply. The physical signs and symptoms do not appear to be consistent with any obstruction of the airway by the engorgement of such a mucous membrane.

Again, early in an asthmatic attack, it is uncommon to find moist signs and expectoration. So any theory of a plugging of the bronchioles with secretion appears to be inconsistent with the physical signs and symptoms of an attack.

There is very much more to be said for the reflex theory. There is no doubt that asthma occurs in persons of the "nervous habit". It has also often been noted that persons subject to asthma who develop attacks in the presence of a rose, will be equally affected by an artificial rose. It may be supposed that the appearance (e.g. colour, shape) of the rose has become a conditioned stimulus grafted on to the basis stimulus of the chemical constituents of the flower. This is an example of a "conditioned reflex". It is also well known that asthmatical attacks may follow indigestion and other alimentary disorders, and similarly respiratory disorders. Experimentally, there is the evidence that stimulation of the upper and posterior part

of the nasal septum will bring on an attack. Emotion has for long been regarded as an exciting factor. And one frequently notices the association of allergic conditions, generally, with variation in function of the endocrine glands.

Owing to the establishment of very much improved technique for recording the movements of isolated bronchi by McDowall and Thornton (6), new light has been thrown on certain facts. It has now been shown that an acid fluid dilates the bronchus and an alkaline one constricts it. In other words, the bronchial muscle is sensitive to slight changes in the hydrogen-ion concentration of the perfusing fluid. Similarly, it is constricted by a slight increase in the calcium or a diminution in the potassium of the calcium-potassium balance. More interesting still is that if the animal concerned is suitably sensitised the isolated bronchi react to minute quantities of antigen. No doubt, this isolated bronchial preparation offers tremendous scope for research.

In 1925, Mudd (7) demonstrated that the expiratory phase was prolonged in asthma. The normal expiration/inspiration ratio is 1:3 to 1:5; in cases of marked bronchial asthma, the

corresponding ratio he showed to be 1:5 to 2:1.

Bronchoscopy has also added considerably to our knowledge of the physiology of the bronchi. They definitely dilate with inspiration and constrict with expiration. These movements have been demonstrated experimentally in man by Hudson (8), using lipiodol. In asthma, the bronchial tubes were shown to be small and their permeability to lipiodol much reduced, the lipiodol failing to reach the bronchioles.

It must now be granted that bronchial muscle spasm is the cause of the bronchial obstruction. The importance of stimuli passing along the vagus from reflex causes must certainly not be overlooked. It certainly seems possible, however, that the vagus may be made more irritable than normal by the circulation of foreign protein, as will be described later on.

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VAGOTONIA AND ASTHMA.

There has been from time to time an enormous amount of speculation on the role of the vagus nerve in the asthmatic syndrome. The names of Eppinger and Hess (9) stamd out predominantly in this subject. Their experiments and suggestions in 1909 have been of tremendous interest, and today there is a distinct revival of interest in the original work of Eppinger.

The Involuntary or Autonomic Nervous System, as distinct from the Voluntary Nervous System, is composed of three divisions:-

1. Cranial Autonomic,
2. Sympathetic proper, and
3. Sacral autonomic.

The cranial and sacral autonomic are referred to collectively as the Parasympathetic system. The sympathetic and the parasympathetic systems may be contrasted as follows:-

1. they are, generally speaking, antagonistic in their action on the organs which they both supply, but some organs are innervated by one division only (e.g. adrenal medulla and most arterioles from the sympathetic only);
2. the excitor cells of the sympathetic are situated, as a rule, at a distance from the

organ innervated, and of the parasympathetic in close proximity to the organs, generally;

3. certain reactions to drugs; the sympathetic is stimulated by adrenaline, the "motor" fibres only of the system are paralysed by large doses of ergotin; the parasympathetic is stimulated by pilocarpine, and paralysed by atropine.

4. both divisions are first stimulated and then paralysed by nicotine.

So that normally, the sympathetic and the parasympathetic, though antagonistic in action, are balanced. Eppinger and Hess experimented pharmocologically with pilocarpine and adrenaline. In normal individuals small doses of these drugs do not cause symptoms. Should there be, however, any loss of balance of the divisions of the autonomic nervous system, exaggerated responses are produced in organs where the two nervous elements act antagonistically, depending upon which division is dominant. Small doses of pilocarpine will give rise to symptoms referable to the vagus, if vagus tone be increased, and small doses of adrenaline will cause sympathetic responses, if sympathetic tone be increased. So arise the two words:-

Vagotonia:- meaning increased vagus tone, and

Sympathetonus:- meaning increased sympathetic tone.

And, of course, it is also possible for there to be an increase of tone of both divisions of the autonomic nervous system, present at once.

In other words, Eppinger and Hess were of opinion that the asthmatic patient was a vagotonic or the subject of excessive irritability of the vagus and parasympathetic. This contention was upheld by Langdon Brown (10) in 1922. It has been stated that practically all diseases tend to produce a disturbance between the sympathetic and the parasympathetic, causing vagotonia on the one hand and sympathetonus on the other. A strong argument in favour of the asthmatic being a vagotonic is the remarkable curative action of hypodermic injections of adrenaline, because thereby is produced the effect of sympathetic stimulation. This point will be referred to again; suffice it to say that the subjects of Addison's disease are not specially prone to asthma.

The classical example of vagal stimulation in man is bronchospasm. Therefore asthmatics

should be classified as vagotonics. If so, injections of atropine should relieve the asthmatic spasms; but such an immediate effect is rare. It has even been suggested that the response to atropine should be used to differentiate between a purely nervous asthma and asthma with an allergic basis; for in the former the paralysis of the vagal nerve endings by the atropine would abolish the spasm which is coming via the vagi from the higher centres; whilst in the so-called allergic cases, there would be no response to atropine as the irritants may be blood-borne, or act locally.

A step forward is promised by the observations of Hurst (11). He maintains that in asthma there is a slight deviation from the average blood chemistry, which results in the vagal constituent of the bronchial nervous system being the predominant partner. Certain chemical, reflex and psychical stimuli, which have no effect in normal individuals, would in such cases give rise to asthma. Whilst certainly explaining the occurrence of asthma from reflex and psychical causes, this theory seems difficult to reconcile with any allergic idea. It seems that Hurst is of opinion

that hypersensitiveness to foreign proteins can only produce asthma in persons with the constitutional tendency, and that the proteins act by stimulating the vagus centre. It has certainly been shown by McDowall (12) that the introduction of some form of protein into some animals causes a greatly increased sensitivity of the vagus. The slowing of the heart and constriction of the bronchi caused by pilocarpine is greatly enhanced by injecting peptone into the blood stream. And it has already been referred to that in some cases foreign proteins may act directly on the bronchi or the neuromuscular terminations of the vagus. The cutaneous reactions or the response of the nasal mucous membrane to pollen cannot be essentially different from the response in the bronchi, and with these it is unnecessary to consider vagus action. Yet the instability produced by proteins is general to the whole autonomic nervous system, including the peripheral vessels. The cutaneous reactions given by proteins also appear to be associated with hyperexcitability of a local nervous mechanism, since they are not obtained if the skin be previously cocainized.

At any rate, it does seem that an absolute

vagotonia, inborn or acquired, may explain why only certain persons are hypersensitive to foreign proteins or other stimuli known to excite asthmatic attacks. To support this there is the well-known hereditary character of asthma and the frequency with which the hypersensitiveness is shown to a group of foreign proteins and not to a single one or to the same one as in the parent, at any rate at first.

It would certainly seem attractive to consider that in asthmatic and allied conditions there are two etiological factors:-

1. the predisposing condition:-
   - (a) vagotonia
   - or (b) a hypersensitiveness to foreign proteins;
2. the exciting cause:-
   - (a) foreign protein;
   - (b) stimuli of mechanical or physical origin.

Yet the same factor may appear to set up both vagotonia and the paroxysm. Compare Gutmann (13) who argues that the irritation of the terminal fibres of the vagus in a fibrotic appendix sets up vagotonia, and that the familiar

symptoms of appendix dyspepsia are those of vagotonia. He quotes a case in which pressure over the appendix immediately brought on an asthmatic attack. Of course, this may be explained as being psychical in origin.

There is no question that the conception of vagotonia is gaining ground. Is the vagotonic person more apt to become allergic, or is vagotonia a manifestation of allergy? Indeed, vagotonia and allergy may prove to be merely different aspects of the one fundamental condition.

In discussing this etiology, it is manifestly important to bring in certain other factors which are of great interest. These are as follows:-

1. the Endocrine;
2. the Nasal;
3. the Toxic;
4. the Nervous or Psychic;
5. the Hereditary;
6. climate, environment and altitude.

ENDOCRINE FACTOR.

Very few subjects have had such varied progress of recent years as Endocrimology. Tremendous enthusiasm has been displayed, often to be very dramatically damped down. Indiscriminate therapeutic exhibition of any substance can never lead to very definite results. And unfortunately, no branch of therapeutics has been so ruthlessly exploited. Therefore, it is important to discriminate in discussing the relationship of endocrinology to asthma and kindred disorders. But there is no doubt that the functional activity of the autonomic nervous system is closely associated with the endocrine glands. Stimulation of the sympathetic will cause an increased secretion of the thyroid, pituitary and suprarenals, and the opposite results will be obtained by stimulation of the parasympathetic. It will serve a more useful purpose to discuss each gland, as it applies, in turn.

Thyroid.

It is in connection with this gland that the commonest endocrine dysfunctions are encountered. Nearly all the observations and conclusions of

the original workers in the subject were arrived at from employing preparations of thyroid therapeutically. With knowledge gained of recent years as to the variability of these preparations, it is necessary all the more to appreciate their efforts. The first observers to put forward the theory of an endocrine origin for spasmodic coryza, as well as asthma, were Rothschild and Levi (14) in 1911. And, of course, they assumed this on the improvement they often obtained when treating cases with thyroid. Since that time, many have corroborated their assumptions. Cases have been described in which thyroidectomy has been of beneficial effect. Asthmatic spasms have been noted in cases of exopthalmic goitre.

With regard to urticaria, writers for many years have insisted that sufferers frequently show manifestations of hypothyroidism and that they derive benefit from thyroid therapy. Others have pointed out that the manifestations of urticaria associated with hyperthyroidism often disappear when the latter is treated.

Fortunately, there is today a very efficient standard of use in endocrinology, not only for diagnostic purposes but also for prognostic.

This is the determination of the Basal Metabolic Rate. And in all cases of allergy in which an endocrine basis is suggested, this should be estimated.

Evidence is certainly accumulating that the thyroid is involved in certain cases of allergy. Discreet observations in diagnosis, prognosis and treatment will often lead to very dramatic results.

Suprarenal.

The effect of adrenaline in relieving the asthmatic paroxysm has already been referred to. In fact, it is almost a specific remedy. So that it is not to be wondered at that Suprarenal inadequacy should be considered a cause. At any rate, it might lead to a relative vagotonia. In Addison's disease, there is a progressive suprarenal destruction, and it is constantly associated with a low blood pressure and intense prostration. But it is only during an attack of an allergic condition that these same two symptoms are found; they are rare during the free intervals. At the same time, it seems unwise to rule out the possibility of an intermittent dysfunction of these glands as contrasted with organic destruction.

The effect of fatigue as shown by the increased tendency for attacks to occur towards the end of each day, each week, or each period of work without holiday, may be attributed to exhaustion of the suprarenals. The sympathetic constituent of the bronchial nervous system needs this adrenaline from the suprarenals; and if it is deficient, obviously the vagal constituent gains the upper hand and the broncho-constrictor fibres come into action. It is well-known that fright may check an asthmatic attack, this being explained by increased activity of the broncho-dilator sympathetic fibres.

Hurst (15) considers that one biochemical factor operative in certain cases of allergy may depend upon the varying activity of these glands of internal secretion. In support of this theory may be noted:-

1. the blood pressure is generally low;
2. many have a well-marked hypoglycaemia;
3. many give a Glucose tolerance curve indistinguishable from that found in Addison's disease;

Sex-glands.

There certainly does appear to be some

association of allergic conditions with increase or decrease in the function of the sex-glands. Boy sufferers undoubtedly tend to improve at puberty. In girls, on the other hand, some allergic condition often begins about this time. And in such a case improvement may be expected at the menopause. The removal by surgery of pathological conditions of the ovaries will often alleviate an asthmatic tendency.

As evidence in support of this association, the fact that asthmatic attacks are often made worse or brought on by menstruation is common knowledge. There must be a disturbance of the normal balance of the internal secretions, which is enough to stimulate the vagus.

The same applies to urticaria. It is often aggravated by menstrual disturbances. Puberty, the menopause and pregnancy may all affect it one way or the other, in some cases causing it to disappear, in others causing it to become much worse.

A most interesting study on pregnancy in allergic patients is that of Williamson (16). In cases actually complicated by asthma, nearly every child showed some allergic manifestation,

such as eczema. A frequent observation also was that there was great difficulty in finding suitable foods for these children. Perhaps the most striking thing of all was that asthmatic attacks did not predispose the mothers to miscarriages nor premature labours. As a matter of fact, many sufferers did not have many attacks during gestation - the latter seemed to lessen the attacks. A notable comparison between his asthmatic cases and his pollen sensitivity cases was that in the latter pregnancy seemed to have no effect on the attacks.

Spleen.

So far as is known today, this is not an endocrine gland, but it is convenient to discuss it in this section. The therapeutic use of splenic extracts intramuscularly in urticaria has brought it to the fore. Splendid results have been claimed, using an extract from which the albumen has been removed.

Irradiation of the splenic area has been tried with varying results in allergic diseases.

In summary, it may be said that the endocrine glands appear to be as fickle here as in any other branch of medical science. Allergic patients in

general do not fall into any picture simulating increased or decreased endocrine dysfunction, at any rate so far studied.

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THE NASAL FACTOR.

The etiology of asthma has for very many years been linked up with Nasal pathology. Rhinologists are only too keen to blame the nose in all cases of asthma. It is, however, a common experience to find but little benefit derived from nasal surgery. Experience is showing that the nasal factor is only a minor cause in some cases and a major secondary effect in the majority of adults. This nasal factor may depend upon:-

1. a blocked airway - this may be due to growths or enlargements acting mechanically; but a complete blockage may also result from any acute inflammatory, chronic hypertrophic or vasomotor disturbance of these narrow passages; in consequence of this obstruction, mouth breathing becomes necessary; and the influx of raw inspired air directly into the bronchi acts as a constant source of irritation to these bronchi;

2. the sensitivity of the "ethmoid region", an area involving the ethmoid, middle turbinal and adjacent parts of the septum and outer wall; Brodie and Dixon (1903) clearly demonstrated

that stimulation of the nasal septum, especially in its upper and posterior part, could lead to bronchial constriction; and it is conceivable that any discharge from infected sinuses may flow over and irritate this area, and that this area may also be irritated by the pressure of polypi, spurs or deviated septa; in other words, the attack in such a case would be truly of a reflex nature.

3. a toxic effect, produced by the presence of sepsis, say from infected sinuses.

Obviously, these factors may be present together. There would then be a kind of vicious circle, leading to the production of gross pathology.

It must be granted that the onset of allergic disease generally occurs in childhood. And yet it is extremely rare for any obvious nasal pathology to be observed in children. In examining 800 allergic children, Bray (17) only found ten cases. Moreover, nasal polypi and sepsis occur just as frequently in persons who show no allergic response. So that there must first be present an allergic predisposition. And as a result of repeated allergic reactions,

enlargement and swelling of the nasal interior occur and eventually give rise to infection. Such a damaged mucous membrane would naturally be more permeable to specific allergens.

As will be noticed, the basis of the nasal factor in the etiology of asthma and kindred disorders is the so-called "ethmoid region". Therefore it is important to describe this in some detail. Its boundaries are:-

anteriorly; the anterior end of the middle turbinal;

posteriorly; the body of the sphenoid and perhaps the sphenoid cavity;

inferiorly; the lower margin of the middle turbinal;

superiorly; the cribriform plate;

laterally; the lateral surface of the nose corresponding;

medially; the septal surface corresponding;

The whole of this area is lined by secreting mucous membrane.

The path of the reflex is intricate but definite. The "Ethmoid region" is supplied by:-

1. the anterior ethmoidal nerve, a branch of the ophthalmic division of the trigeminal;

2. branches of the maxillary division of the trigeminal via the spheno-palatine ganglion;

Sensory impressions gathered from the area by these two nerves pass along the sensory portion of the trigeminal and down its descending root, as far as the neighbourhood of the nucleus ambiguus. This is an elongated column of grey matter which extends downwards through the medulla oblongata and becomes continuous with the anterior column of grey matter in the spinal medulla. From it arise the motor fibres of three cranial nerves, in order from above downwards, the glossopharyngeal, vagus and spinal accessory. The arrival of the sensory impressions in the neighbourhood of this vagus nucleus gives rise to stimuli, which travel down the vagi to the anterior and posterior pulmonary plexuses; and bronchospasm results. And this is what is described as the naso-pulmonary reflex. That such a connection does exist between the ethmoid region and the bronchial musculature has been verified by Myers (18) who showed:-

1. that bronchospasm could be readily induced by mechanical irritation of the ethmoid region, in susceptible persons;

2. that cocain applied locally to this very area

will relieve a spasm so induced:

3. That there is a distinct tendency for the bronchospasm to be present on the side corresponding to the side of the nose experimentally irritated.

This latter observation he would emphasize by pointing out that persons with definite nasal pathology on one side usually have bronchospasm on the same side.

Perhaps it is not unnecessary to repeat that the importance once attached to nasal abnormalities is not so marked today. When such abnormalities are found, they are regarded more as coincidences or as results of allergic manifestations of the nose. It can be quite readily understood how repeated allergic attacks would lead to thickening of the mucosa lining the various sinuses that drain into the nose, and so obstruct these channels as to convert these sinuses into fertile fields for bacterial invasion and growth. Then would arise the question as to whether subsequent reactions would not be examples of bacterial allergy.

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THE TOXIC FACTOR.

For long it has been maintained by many that asthma was primarily a toxic condition. In fact, this theory has been advanced as a rival to the whole subject of allergy. It has two great exponents - Haseltine and Adam. The latter (19) maintains that the sources of the toxin are (a) the bowel and (b) the nose. The nasal factor has already been dealt with. It now reamins to investigate the part played by alimentary toxaemia. Many well known aspects, of asthma particularly, will need consideration. To support his contentions, Adam points out:-

1. the high percentage of week-end periodicity - stated to be 60 per cent;
2. the presence of a sallow skin and cachectic appearance in many patients;
3. the age of onset of attacks, at a time when infectious diseases generally are most common, namely at puberty;
4. the relief often obtained when environmental conditions and mode of living are changed, such, for example, as joining the Army.

On the other hand, intestinal toxaemia, so-called, and nasal diseases are quite common compared with asthma. It is only in those cases where the person is allergic that these factors will give rise to the Syndrome. The question of Food Allergy does not apply in these cases. It will be described subsequently. Actually, it is the general principles of the diet that come under this heading of toxaemia. It would seem that quantity matters more than quality. Big meals cause gastric distension and may thus reflexly produce an asthmatic attack. This is substantiated by the relief obtained from vomiting. In many cases, defaecation will also give relief; and in such instances, rectal distension must similarly be acting reflexly.

Next, asthmatics soon learn the wisdom of never having late meals. A lapse in this direction will nearly always have an attack as the inevitable result.

It would seem that certain articles of food and the mode of cooking are also involved. Harrington (20) is of opinion that milk is particularly prone to initiate attacks. Cooking

in fat is undoubtedly bad for allergic individuals. Even beverages that contain fat, like cocoa, have a decided detrimental effect. Bananas and tomatoes are the worst enemies of many allergic persons.

Another important point is that the same article of food may have different effects at different times. In the case of such as milk, this would seem to depend on how the cows are fed.

Food Allergy.

This is a subject of great practical importance because it involves:-

1. The introduction of allergen to produce active sensitisation, and
2. The production of symptoms in individuals already sensitised.

Sensitisation through the digestive tract was first demonstrated by Rosenau and Anderson (1908). They mixed egg-white in the food of guinea-pigs and later demonstrated shock when these same animals were inoculated, intraperitoneally, with a solution of egg-white. Discussion of the whole subject would be out of place without a reference to a monograph by Laroche,

Richet and Saint-Girons (1919) called "L'Anaphylaxie Alimentaire". This has been translated and republished in English under Rowe (1930). It is full of information and suggestions. It confirms the experiments of Rosenau and Anderson in guinea-pigs. Secondly, they maintain that in an animal or man already sensitised, the ingestion of food can produce symptoms.

Food allergy includes all reactions arising from the ingestion of wholesome and normally well-tolerated foods. The sensitivity may arise from handling foods, as well as from their consumption either in a cooked or raw state. A very interesting observation is the variation in manner of onset, site of election and duration of symptoms, which appear to depend on whether an usual or unusual article of food has been eaten. If it is an unusual food, the attack is generally acute and short, in duration, and involves first the stomach and then the colon. If the food is a commonly used one, the symptoms are generally chronic and continuous, and colonic in origin, either as a result of excessive peristalsis and mucous secretion or constipation with symptoms of general toxaemia.

There is no doubt that food allergy is most frequently encountered in children. It characteristically disappears with advancing age, or at any rate becomes much less marked. Whenever difficulty is experienced with children and infants concerning food, it is wise to inquire carefully into the family history. It is surprising how very often this turns out to be of an allergic nature. Particularly does this generalisation apply to the symptoms of anorexia, a very common reason for consultation about a child. It must be remembered that food allergy occurring in later life almost invariably had its origin during the first decade.

At any rate, gastrointestinal absorption is well recognised now. It seems to occur in most cases only when the intestinal mucous membrane is injured or weakened in some way, as by overfeeding, enteritis or some disturbance of digestion.

Urticaria, eczema, asthma and rhinitis are well known results of food sensitivity. But occasionally, other symptoms may result. Of these, it is important to mention a general reaction to shock - labelled by the French "La Grande Anaphylaxie Alimentaire".

It is characterized by vomiting and severe abdominal pain, accompanied in most cases by urticaria. The importance of the condition lies particularly in the fact that it is apt to be mistaken for an acute surgical emergency, such as appendicitis, should the urticaria be absent. Attacks of this kind more often occur in those children sensitive to egg. Minor attacks of this description certainly do occur. And a recurrent and chronic mild type is described, in which pain and diarrhoea occur together without any obvious cause.

Under Toxic Factor it would be as well to discuss the parts played by Syphilis and Tuberculosis.

Syphilis.

Several investigations have been made on this subject in its relation to allergy. It would appear that the association is a mere coincidence. If improvement does follow arsenical treatment, it no doubt results from the improvement in the general health of the allergic individual. The same may be said regarding hereditary syphilis.

Tuberculosis.

This is a subject - the relation of tuberculosis to allergy, particularly asthma - in which

there appears to be some difference of opinion. And it is a very important one, because it is a popular superstition that asthma is a manifestation of tuberculosis. Now, there certainly is no doubt that tubercular patients do develop asthmatic symptoms. Rackemann (21) states that the incidence of tuberculosis among asthmatics is considerably higher than among normal people. Cases have also been reported in which the onset of asthma has converted inactive tuberculosis into an active type. Bray (22), on the other hand, is of opinion that if an asthmatic becomes tubercular, the tuberculosis develops independently of the asthma. It is worth while to probe the matter further. First, many tubercular patients with asthmatic symptoms are certainly not suffering from asthma; the dyspnoea is purely mechanical and bears no relation to sensitivity. Secondly, cases of tuberculosis may become fibrotic and develop a type of bronchitis, which is asthmatic; such cases developing asthma would not appear to differ from those cases following pneumonia, say; sensitisation and asthma then follow tissue damage. Thirdly, it must be remembered that tuberculosis is very apt to

follow measles and whooping-cough in children. In other words, tuberculosis and asthma are given most favourable opportunities to develop at the same time. It has been known for some time that the proteins of the tubercle bacillus are not capable of producing such allergic manifestations as asthma. On the other hand, the secondary bacillary invaders of tuberculosis cavities are a very important consideration, and involve the subject of "bacterial allergy", which will be discussed subsequently. Finally, especially in children, many cases of asthma have been erroneously diagnosed as tuberculosis. And it is well known that cases of pulmonary tuberculosis, diagnosed clinically and by X-rays, complicated by asthma, can be relieved of their asthmatic attacks if proteins to which they are sensitive are removed. The tuberculin reaction very often indicates the presence of a latent tubercular focus and not active tuberculosis. Comparing, in children, the age of incidence of asthma with the relative incidence of positive tuberculin tests in the same children, it is noteworthy that the latter shows a gradual increase in percentage as age advances, and the

former a gradual decrease.

And so it does seem that no definite relationship exists between asthma and tuberculosis, and that tuberculosis does not play a part in most cases of asthma and allied conditions.

Before leaving this question of the toxic factor, the various ideas on Tissue Damage must be referred to. It becomes of very great interest where etiology is concerned. Local tissue damage would seem to explain many allergic phenomena:-

(a) migraine occurs in people suffering from eye strain;

(b) eczema chooses sites exposed to damage from wind, washing or sweating;

(c) effusion occurs into a damaged joint;

(d) asthma often follows whooping-cough, measles or pneumonia;

(e) eczema may occur in housewives or bakers who are sensitive to flour;

(f) and so on.

One observer, Freeman (23) attempts to determine the site of allergic response with the theory of local tissue damage. There is much to support

this, such as the conjunctivitis of the pollen-sensitive person to his specific pollen. The "patch test" further enhances this view; in this, irritants, often of a non-protein nature, are placed in apposition to a patch of skin; and in sensitive persons a patch of eczema results after twenty four hours' contact. This idea is not in agreement with that of Coca, who thinks that once the protein irritant has passed through the skin or mucous membranes into the blood stream, reactions will tend to occur in any part which has become sensitised through previous contacts with the protein - in the bronchioles leading to asthma, in the skin leading to eczema, in the brain leading to migraine, and so on.

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THE NERVOUS FACTOR.

For over a century many competent observers have regarded asthma as being of nervous origin. Various theories were put forward to explain how the nervous system was implicated. For instance, Salter in 1868 thought that the bronchospasm of asthma was the reflex result of a pathological condition in the nervous system. Of more recent interest is the publication in London in 1915 of a monograph, called "Nervous Asthma," by Berkart (24). The latter recognises the inherited nature of asthma, but he states that asthma has an endogenous neuropathic basis. He regards asthmatic attacks as anxiety neuroses, due to the fear of an impending dyspnoea. There is an ingenious theory as to why the respiratory organs should be specially picked out in such a neuropathic diathesis; it is, that there is in such a case a history of a severe attack of some acute infective process during childhood affecting the air passages, in which the child was very ill and recovery was protracted and incomplete. Since the publication of the monograph, however, much evidence has accumulated to undermine these

theories. It has been shown that allergic reactions frequently occur in tissues such as the central nervous system, which cause patients to react in exaggerated ways to sensations and specific impressions. In fact, this is often to be observed when taking a history of an affected child from an allergic parent. Moreover, it is not uncommon to see a complete change of personality during an allergic attack. These facts have been well brought out by Duke (25). And it is now well recognised that if the allergic factors in nervous children are removed, the nervous state shows great improvement. Emotions such as grief and worry are presumable predisposing factors upon which the allergic state develops. Expectation is regarded by Hurst (26) as the most common psychological factor in asthma. Even when the original chemical or reflex cause has ceased to operate, anyone who has been in the habit of having attacks under certain circumstances or in certain places is quite likely to do so again. This is, however, the result of auto-suggestion; and over activity of the bronchi will only occur in asthmatics, under such circumstances. Expectation would seem also to account in part for the

relief from attacks such a large percentage of asthmatics obtain when moved to a hospital - that is, the expectation of benefit to be derived. At the same time, such a case is being freed from the presence of the specific allergen of his home. Some emotions, such as sudden fear and anger, may suddenly stop an attack; this must be the result of the flooding of the system with adrenaline. Hurst's contention about expectation producing an attack may be regarded in another light, namely, it may be a conditioned reflex. Granted that the attacks will occur without the intervention of any specific allergen, they will, however, not occur in persons who are not already allergic. This can be confirmed by the Prausnitz-Kustner reaction. Any attempt at a classification of such a subject as asthma and the nervous system must be welcome. Hence it is well to quote Gillespie's (27) three categories:-

1. cases in which the attack appears to have the same status as a neurotic symptom;
2. cases in which the asthma is independent of a co-existing neurosis, but in whom

emotional causes may precipitate an attack;

3. cases in which the nervous systems are definitely secondary to the disability.

Most cases certainly would appear to belong to the two latter groups. Cases of the first category must be extremely rare.

At various times hypnotism and psycho-analysis have been employed in treatment, with claims of successes few and far between.

The contemplation of nervous asthma is dangerous ground. . It has been repeatedly found that many cases of so-called nervous asthma have been cured by a new residence, new furniture or new environment generally, and different living conditions. When the cause of the disease is simple - an egg in the diet or a cat in the house - the relief is so prompt following its removal that nervous factors must be excluded. Most individuals would be "nervous" if their sleep were interrupted once or twice every night. As a matter of fact, the bronchospasm commences most often during sleep, and many asthmatics, on waking, find themselves already sitting up in bed, on account of the dyspnoea. It is this difficulty

of breathing which they first appreciate. Children will often sleep through a mild attack. And it is impossible to get away from the fact that both the age-incidence and the sex-incidence of the psychoneuroses and asthma are quite different. The psychoneuroses occur in women in middle life, asthma in young boys, generally speaking. In the same way as it would be futile to argue that all cases of asthma are due to gastric or rectal distension, so it would be to say they are due entirely to psychopathic states. But it is possible that any nerve strain may increase the hypersensitiveness of an individual, provided that individual is already subject to these responses. A balanced allergic state may conceivably become upset by exhausting and depressing mental states, exposing the body to the action of allergens. Sometimes allergic individuals seem able to stand the presence of allergens and show no symptoms; at other times they develop a violent attack. So that the view, held by the French, that there is a disturbance of vago-sympathetic balance may be the solution of the problem. It does seem that the secret may be a decrease in the normal secretion of adrenaline.

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THE HEREDITARY FACTOR.

This is of such practical and clinical importance that its discussion will be deferred to a separate section of its own.

CLIMATE. ALTITUDE. ENVIRONMENT.

There is no more capricious thing about allergic diseases than their behaviour regarding locality and environment. Some cases do well by the sea, others not. Some cases do well in large smoky cities, others not. It seems almost impossible to foretell exactly what will suit any individual case best. In the home, it is extraordinary how persons may become sensitive to practically anything. The kind of atmosphere, the kind of soil, the kind of climate and so on; all are implicated. The one constant factor is that if relief does occur from any change of climate, altitude or environment, it must be prolonged if benefit is to be expected; for relapse will most certainly occur on return to former conditions.

Most allergic conditions will subside above an altitude of 4,500 feet; this may be due to:-

1. Changes in the individual biochemistry.
2. Removal of the specific allergen; and to

3. Expectation of benefit to be derived.

Hurst states that at least 90 per cent of asthmatics lose all or nearly all their symptoms by residence at a height of over 4,000 feet, and that these symptoms disappear within a very short time of arrival. Children derive far more lasting benefit than adults. For whereas attacks tend to recur in adults on their return home, in children a permanent cure may often result; provided, of course, the period of residence has been of sufficient duration. The significant point about this relief from attacks by altitude is that those factors which would induce attacks at home now seem no longer able to do so. And yet there is no deficiency of pollen. Sage is said to be plentiful. It is well known in the Air Force that flying sufficiently high will give relief to asthmatics. This temporary immunity from attacks may be due to changes induced in the biochemistry of the blood as the result of anoxaemia.

In discussing the subject of environment especially as it applies to the home, the name of Van Leeuwen (28) is foremost. An enormous amount of work has been done by him concerning

house dust in particular. He maintains that in Holland 90 per cent of patients with asthma are hypersensitive to allergens contained in the air, these allergens being absorbed through the mucous membranes of the air passages. It appears that the house dust from anywhere in Europe contains a common allergen, which only varies in prevalence with increasing heights above the level. Eighty per cent of asthmatics give positive skin reactions to this house dust. Van Leeuwen investigated the nature of this house dust and found that the most important parts were the products of destruction of micro-organisms, moulds and insects. These have been called miasms. Having got so far in his investigations, he proceeded to see what effects would be obtained by freeing patients from these miasms. To do this, he had to construct dust-free houses, the air for which is drawn down through a chimney thirty-five meters high and then through a cotton filter. A modification soon followed in the construction of "Allergen-proof chambers", in which the beds were of iron, pillows and mattresses of kapok and the blankets woollen,

and which were of course air-tight rooms, ventilated as described above. It is important to note that the air before entering the chamber is purified by cooling and then heated. In this environment, Van Leeuwen claimed that a large proportion of his patients have recovered quite promptly , after three to four days, from their symptoms. He is of opinion that these chambers have three advantages;-

1. they are of use in diagnosis - as by their use purely climatic cases can be differentiated from food and other allergies;
2. they are of use in prognosis - judging by the improvement obtained in their use;
3. they are of use in treatment.

Various dust-free contrivances have since been invented. The point about them all is that they are only of use in selected cases. It is impossible to overlook the large number of asthmatics that gain relief from simple admission to a hospital or home. At any rate, it seems probable that such air-filters would be of most use during the hay-fever season in pollen allergy. And of course, a mask of sufficient protection must undoubtedly be of great benefit

in occupational asthma, as in bakers.

There is a type of case in this country which is of great urgency, and in which environment is of foremost importance. This is the asthmatic child in an underfed and overcrowded family. The child is subject to repeated and continual infections. The parents cannot afford to buy separate pillows, mattresses and all such items, and thus remove all specific allergens. The asthma is probably secondary to severe lung damage. Desensitisation may be incomplete and may even fail. The ultimate result is the early onset of a deformed chest and marked pulmonary over-distension. In such a case, special convalescent homes are of very great importance. The results obtained are often astounding. In this country, the best situation for such a home appears to be westward of Lancing, in the south of England. In America, Peshkin (29) is doing his best to stress the value of convalescent homes in suitable climates for children. His statistics definitely emphasize the benefit to be derived. There is no doubt whatsoever, that the establishment of homes where chronic refractory asthmatic children

can be kept and treated for a period of at least six months is an urgent and economic necessity. The most suitable soil for asthmatic patients would appear to be sand, chalk or rock.

A short reference to spas and resorts will not be out of place. From personal experience, Hurst (30) has been able to show that they are of definite value in many cases. He considered that most benefit accrued from inhaling vapour containing a considerable quantity of free carbon dioxide. This led him to improvise an apparatus for home use, with which he claims the same beneficial effects may be obtained. One thing about all spa treatment must not be lost sight of. It applies just as much in all allergic diseases as in any other branch of medicine. That is, the routine. This comprises regularity of meals and treatment, hot baths, showers, gargles, foot baths and complete mental rest. The psychological factor is ever present where patients discuss their improvement with each other and where the doctor is frequently and regularly seeing and consulting with them.

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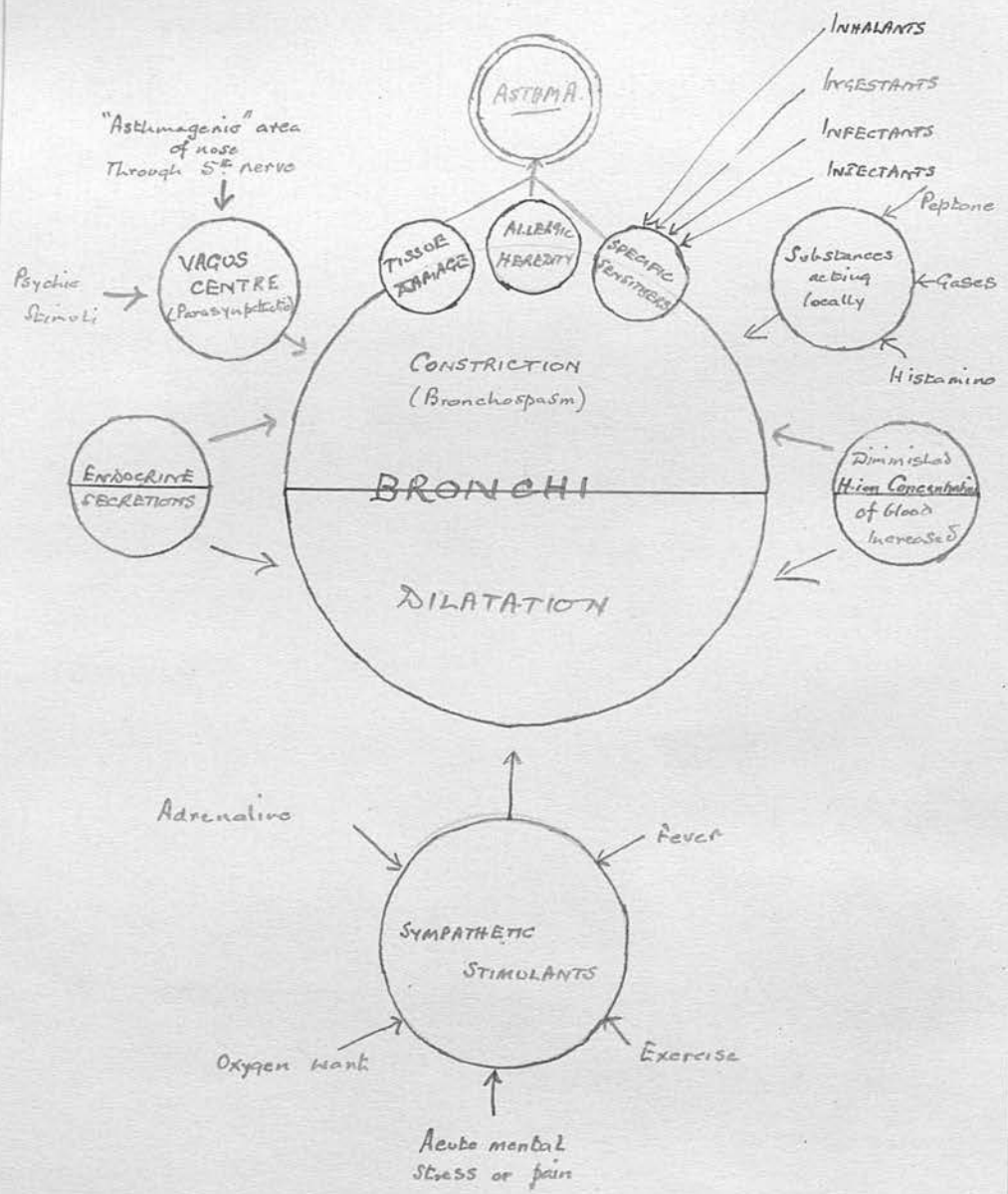
ASTHMA AND ALLERGY.

Allergy is the term used to indicate the altered capacity with which certain human individuals react excessively to contact with particular substances. And an individual is said to be allergic when he has this capacity to react. In many cases, the relation between the symptoms and the causative agent is clear-cut, as in asthma brought on by contact with animals. In other cases, it may be obscure and the onset of the trouble occur some time after exposure. The causative agent producing symptoms may be "extrinsic", that is outside the body, or "intrinsic", that is arise within the body. The former agent is of the type of animal or plant emanations, the latter due mostly to infections, for example, it is quite common to find patients who develop allergic symptoms only when they have a "cold". Although the relation of allergic symptoms to these infections is not always so clear as in the extrinsic group, yet bacterial hypersensitiveness plays a very important role. At any rate, in each of these various cases, the individual is hypersensitive



GENERAL ETIOLOGY OF ASTHMA IN DIAGRAMATIC FORM.

to a substance, of varying chemical structure, contact with which produces any one of a number of different clinical pictures. These different clinical conditions have, however, certain very definite characteristics in common. To recapitulate there are:-

1. a presenting symptoms which is characteristic, such as asthma;
2. a history of other allergic manifestations in the same person, such as eczema in childhood;
3. a family history of allergic symptoms usually in the antecedents;
4. ability of skin or mucous membranes to react positively to foreign substances "specific allergens", when applied;
5. eosinophilia in blood;
6. response to adrenalin.

Now, asthma must be regarded as denoting a symptom. It should be looked upon in the same light as "headache". It represents a very definite symptom complex, such being capable of production by a wide variety of different causes. This symptom complex is characterised by breathing of a peculiar wheezy character, due to an obstruction of an easy flow of air in and out of the

chest. Between attacks of this nature, the patient is essentially well, and can breathe in a normal manner.

In order to demonstrate the connection between allergy and asthma, it is essential to attempt some classification of asthma so that all cases can in due course be brought into line with the general principle. There are two principal ways in which asthma can be classified, (a) according to etiology, and (b) according to pathology. Neither classification is wholly satisfactory, partly because the diagnosis of the etiology and the clinical estimation of the pathology are both difficult, and partly because no one of the groups is entirely distinct and each of them shades into other groups to a greater or less extent.

In the Etiological classification, account is taken of the following:-

History,

Physical Examination,

Skin Tests,

End result two years after examination.

It is then possible to divide all cases of asthma into three groups:-

Extrinsic - cases hypersensitive to some foreign substance outside the body, who develop asthma on exposure to such;

Intrinsic - cases hypersensitive to some substance elaborated from within the body;

Mixed or Unclassified - cases which cannot be definitely placed in one or other of the above.

The extrinsic cases, then, are due to pollens, animal emanations, environment, food, and so on. Intrinsic asthma includes bacterial cases, reflex cases due to nasal and throat conditions, reflex cases other than those due to the nose and throat, and so on. In the bacterial group are cases whose asthma only occurs after some acute respiratory infection which may happen at very long intervals, the important point being that the patient is living in the same environment with the same occupation and on the same general diet at all times. Such individuals are perfectly well between attacks and show no chest abnormalities. Reflex cases are those in which there is present a focus of infection in the nose or throat, teeth, gastro-intestinal tract or

elsewhere, in which cases, because of improvement following treatment of the focus, such foci can be regarded as direct causes of the asthma. In this group it is possible to place patients with obesity and other general disturbances, which seem to have a very definite bearing on the cause of the trouble.

Many authors have ignored the existence of intrinsic asthma because they maintain that every case of asthma depends upon a hypersensitiveness of the patient to some foreign substance which may be unidentified as yet. As the variety of test substances is gradually being extended it is unwise to ignore such a contention altogether.

Bacteria can produce asthma in three ways. First, asthma may depend upon a direct sensitiveness to some bacterial product. There is a type of case in which one or two attacks occur during the year without any change in occupation or diet but in which there is a definite association with an acute respiratory infection. Insuch, it seems reasonable to assume that the bronchial spasm is dependent upon the infection.
Secondly, where a patient is not

very sensitive or where the exposure to such particular allergen is not heavy enough to cause the symptoms of itself, an infection may cause symptoms to appear after exposure to such particular allergen. That is, an infection by itself may not produce the asthmatic attack, nor may exposure to the particular allergen. The combination of the two at one and the same time may, however, result in the production of symptoms. And in those patients with positive skin tests to various foreign substances, a new infection may result in bronchospasm, which may be due to the fact that the occurrence of the infection has in some way modified the degree of sensitiveness to the allergen. Thirdly, bacteria may intensify and prolong an attack of asthma which has started from any cause.

Among the reflex causes, it is interesting to discuss the "gall-bladder type", which is seen chiefly in women. The symptoms are persistent from month to month and from week to week; these cases are always short of breath and

rarely sleep through the entire night. Most of them are cyanosed. In spite of the persistence and severity of their symptoms, they remain well nourished if not obese. In most of these cases the common symptom complained of is indigestion, with flatulence and persistent epigastric pain. In spite of the history and clinical condition, it is, however, a fact that gall-stones and gall-bladder conditions are rarely found in such cases. X-rays will show a low diaphragm with limited excursion, and perhaps a thickening of the lung roots.

This subject would be incomplete without a reference to Cardiac asthma. It is not always easy to exclude the ordinary causes of asthma in such cases. Even if the asthma corresponded in onset with the heart disease, the predisposition to asthma may have existed in the patient beforehand, and this may express itself as an unusual irritability of the finer bronchi or perhaps as an arteriosclerotic process. There are three theories regarding cardiac asthma.

First, a failure of the left ventricle diminishes the output from the lungs and thereby causes stasis in the pulmonary circuit and in the whole venous system. This accumulation goes on until perhaps the congestion and enlargement of the bronchial mucous membrane induces bronchospasm, in bronchi perhaps unusually irritable. When the patient sits up, the stasis is relieved and the attack passes off. Secondly, there is a theory that marked congestion of the lungs may also be due to failure of the right ventricle. It is difficult to conceive this without a left-sided failure also. The difficulty with both these theories is that pulmonary congestion is common in broken compensation from any cause; and yet of the many patients who have it, only a very few have asthma at the same time. The third theory is of long standing and depends upon the fact that stimulation of the aorta can produce bronchospasm. It has been shown also that patients with cardiac asthma frequently have arteriosclerosis. So it seems reasonable to assume that the bronchospasm of cardiac asthma may be due to a reflex effect from aortic irritation.

So many patients with asthma have well d

defined lesions in the nose, throat or sinuses that various authors have considered that the bronchial spasm was merely a reflex effect of some local stimulus arising in the upper air passages. The course of the reflex has been already discussed. That treatment of such nasal and throat conditions is notoriously disappointing in its results is well known to clinicians. In fact, the large number of patients with asthma, who return for treatment with a story of previous operations on the nose and throat, is very impressive. A careful study of this subject lends considerable support to the idea that the clinical lesions found in the sinuses, nose and throat are merely a part of the fundamental pathological changes that occur in asthma. That these lesions are not found in every case does not exclude such a contention, because they may well represent the end result of a process, which in its beginning is hard to recognise. At any rate, it is very difficult to actually decide whether these local lesions cause symptoms by being the source of some bacterial poison to which the patient is

hypersensitive and to which he reacts as to any other allergen, or whether the local process does, by a true nerve reflex, produce bronchospasm.

A classification of asthma based on pathology is unsatisfactory for two reasons:-

1. it is uncommon for a patient to die of asthma; so that the opportunity to check the clinical conception of the lesion by an autopsy is rare;
2. it is very difficult to define accurately the various types of asthmatics, because intermediate varieties of every type can be recognised and because the type in any one patient is apt to change with the occurrence of new infections.

Having thus discussed the question of classification and outlined the mode of operation of intrinsic, reflex and other cases, it is possible to realise that:-

<u>Asthma is a manifestation of Allergy,</u> at any rate in most cases. Most asthmatic patients present many of the criteria for allergy, which have been defined. And more important is the fact that attacks of asthma come and go according to exposure to some particular foreign substance to which the patient is hypersensitive.

Anaphylaxis.

As an introduction to this subject, it is helpful to recall the subject of anaphylaxis in animals. For it is inevitable that the condition of an allergic individual should be compared to that of the anaphylactic animal. Allergy is the capacity to react to many substances which are entirely innocuous to normal individuals. The anaphylactic animal reacts to a dose of a substance which is harmless to a normal animal. The capacity to react in such a characteristic way must obviously imply some change in the individual to make him react violently to slight contact with harmless substances; in other words, it must make him hypersensitive.

The fundamental facts of anaphylaxis are as follows:-

1. guinea-pigs will become sensitised to that particular protein substance with which they have been treated parenterally, even in minute quantity;
2. if the guinea-pigs are then allowed to rest for a period of seven to fourteen days - an incubation period so to speak - sensitiveness will develop and can be demonstrated by further

parenteral administration of the same substance;

3. this second dose of the same protein will cause severe symptoms in the sensitised animal, even though it be given in amount well below that necessary to produce symptoms in a normal animal; this reaction is highly specific in that

(a) the substance used must be the same as that to which the animal was sensitised, and

(b) the isolated tissues of the sensitive animal will also react specifically to treatment with the specific protein; thus, the guinea-pig uterus, suspended in a bath of Ringer's solution, will contract when the protein is added to the bath; this is the Dale (31) reaction and is used as a test for hypersensitiveness;

4. the blood serum of a sensitive animal has the property of transferring the state of sensitiveness to a normal animal. This reaction is also highly specific, in that the animal receiving the serum and passively sensitised will react only to the particular serum; this is Passive Anaphylaxis;

5. the animal can be desensitised, and is then in a condition of anti-anaphylaxis, by giving it

a second dose of the particular protein substance, sublethal in amount; but such a state is only temporary and the animal will eventually again be hypersensitive;

6. A peculiar reaction is observed practically only in rabbits, called the Arthus Phenomenon, in which reinjecting a sensitised rabbit with the specific protein will lead to very extensive local reaction.

These six facts are of great importance in the study of human hypersensitiveness. The anaphylactic reaction is said to occur in one of two sites, either in the circulating blood or in the tissue cells. So that there are two theories as to site, and they are called:-

(a) Humoral, referring to the site as being in the circulating blood, and,

(b) Cellular, if in the tissue cells.

They have been advanced as the result of the injection of a foreign protein into an animal, which results in the production of antibodies in the blood stream and of antibodies attached to the cells. The phenomenon of passive anaphylaxis gives greatest support to the Humoral theory - for obviously the agent must be in the blood, if anaphylactic blood can transfer sen-

sitiveness to a normal animal. On the other hand, the upholders of the Cellular theory claim that the recipient animal does not become sensitive at once, because the antibodies do not become effective until they have had time to become attached to the cells of the recipient animal. Moreover, the Dale reaction appears to be a definite manifestation of the presence of cellular antibodies, although this also has met with adverse criticism. At any rate the principal reaction in anaphylaxis takes place in the cells or on their surface.

The symptoms of anaphylaxis vary in different animals. To explain this diversity, it would appear that the different effects depend upon anatomical and physiological differences. The chief of these is the varied distribution of non-striated muscle in the different species. Another very important point is the ease with which different animals can be sensitised and the regularity with which the symptoms of shock can be produced by re-injections. The phenomenon of anaphylaxis occurs in animals that have been prepared by a previous injection. The phenomenon occurs in men without preparation, and so is "natural".

And the mode of sensitisation is not the same in animals and man. For in the former, a previous parenteral introduction of a dose of the protein is necessary and is followed by a definite incubation period. In man, on the other hand, hypersensitiveness usually develops slowly and insidiously, and frequently follows prolonged and repeated contact with the particular substance. It is also noteworthy that sensitiveness in man is not usually restricted to one particular substance, but is usually manifested towards a variety of substances. And the degree of sensitiveness in man is far more delicate than in animal anaphylaxis. As regards desensitisation, in anaphylaxis this is definite; in human hypersensitiveness, it is much less clear cut. Even when a general reaction follows injection of the specific substance in man, no desensitisation can be demonstrated, and the same reaction will occur day after day if exactly the same dose be each day employed.

Now, the typical experiment of anaphylaxis in animals can only be produced with proteins, that is, with substances which:-

1. can be coagulated by heat;
2. precipitated by ammonium sulphate and alcohol; and

3. give a positive biuret reaction.

A detailed study of proteins from plants and vegetables - purified, of course,- brought to light the fact that crossed reactions could occur between them, so that an animal sensitised to one would react with anaphylactic shock to a later dose of another. In 1929, Goebel and Avery (32) published some very important researches in which they showed that they could produce active and passive anaphylaxis by injecting animals with sugar-protein complexes, and that there was a definite specificity between them. These bodies they obtained by attaching animo and phenol groups to simple hexoses. Further recent observations would seem to attach much importance to the carbohydrate constituents of some proteins. Various attempts have been made to find out whether or not the part of the protein molecule responsible for the production of sensitiveness is different from the part concerned with the intoxicating effect of the second dose. So far, however, it may be said that the chemistry of anaphylaxis is unknown in its essentials. It certainly depends upon

complex protein substances. The sensitising and intoxicating powers are reduced by heat and chemicals. The essential principle may be assumed to contain at least one aromatic radicle in its formula. The fact that the symptoms of anaphylactic shock are the same by whatever produced suggests the formation of a poisonous principle which is the same in each case. And various interesting researches have been made to try and discover such a substance. These researches are the foundation of the various theories regarding anaphylactic shock, which theories and views may be grouped together under various headings; toxic, physical, organic, proteolytic and histamine.

Toxic Theories.

In 1902, Richet advanced the theory that the union of antigen and antibody gave rise to a very poisonous substance, which was called apotoxine, and that this substance produced anaphylactic shock. Friedberger (1909) modified this, and maintained that precipitin resulted from this antigen-antibody union, and that this combined with certain substance in the circulating blood to form anaphylatoxin, which caused the symptoms of anaphylaxis.

Physical Theories.

That the antigen-antibody reaction led to physical disturbances in the blood has been claimed by many Continental observers, such as Bordet (1913).

Organic Theories.

In the opinion of Besredka (1907) the antigen-antibody union was so violent as to disturb the equilibrium of certain nerve cells at the site of the reaction. A disturbance of the functions of the liver has also been claimed as being responsible for the production of anaphylactic shock.

Proteolytic Theories.

Vaughan (33) was trying to discover the poisonous element in bacteria when he discovered that the use of a substance, which he called protein poison, and which he had obtained by extraction with alcohol from massive bacterial cultures, could produce anaphylactic symptoms. Jobling and Petersen (34) suggest that proteins are split up slowly and harmlessly by enzymes when introduced for the first time parenterally into animals, and that this leads to the

development of a large quantity of specific enzymes, which are capable of splitting protein rapidly so that later injections of the protein are likely to be followed by a quicker liberation of toxic products, which result in anaphylaxis being produced.

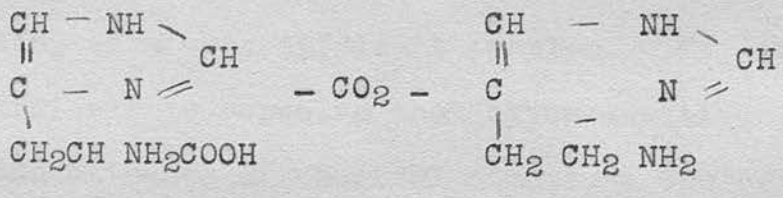
Herb (35) has modified this theory of Vaughan's and considers that anaphylaxis will follow a deficiency of complement or of ferments.

The intravenous injection of peptone produces symptoms which have a striking resemblance to anaphylaxis. This was first noticed by Briedl and Kraus in 1909. A concentrated substance has been extracted from peptone, called vasodilatin, which is said to be the causal agent. The symptoms produced thereby can be controlled by adrenaline. It is interesting to record that animals can be partially desensitised by treatment with peptone. Peptone shock causes a loss of coagulability of the blood, thus resembling very closely anaphylactic shock.

Histamine Theories.

Dale and Laidlaw (36) showed that after an injection of histamine the blood accumulated in the widely dilated peripheral capillaries, from which there was extravasation of fluid and

and consequent oedema. In other words, the essential feature was a capillary paralysis with excessive capillary permeability. The fall in blood pressure was therefore a result of the diminution in the output from the left side of the heart. So that the condition was more like traumatic shock with vasomotor paralysis. The action of histamine is also different from that of true anaphylaxis in that histamine is still able to produce a strong reaction in the uterus even though this strip has been desensitised by treatment with specific serum. Now, histamine is formed from histidine by the splitting off of a molecule of CO_2.



(Histidine) (Histamine)

Barger and Dale (37) were the first to isolate histamine as an active factor from ergot. Later they isolated it from the mucous membrane of the gut. It has now been definitely extracted from the gut, liver, lung and posterior lobe of the pituitary. It is of such importance that it will be referred to again.

So far then, the discussion has concerned

anaphylaxis as produced in the experimental animal by proteins. Now these substances require the action of antibodies or ferments to split them in preparation for absorption by the cell. Man and animals, however, can become sensitive to substances which do not require this antibody reaction. Various experiments have been made to support this, a matter of great practical importance in discussing hypersensitiveness in man. The symptoms of the hypersensitive man are essentially the same whether they be due to a protein like egg-white or whether they be due to aspirin. Zinsser's (38) ideas as to the fate of foreign substances entering the body help in the understanding of a very difficult problem. For it is difficult to conceive that hypersensitiveness to such extremes of chemical structure can be explained on any one basis. He is of opinion that foreign substances entering the body are disposed of in two ways:

(a) either they are absorbed into the cell for the cell's nourishment, or

(b) they are absorbed in order that in the cell they may be broken down into simpler substances and eliminated.

Substances like aspirin are diffusible and

enter the cell directly, and do not need antibodies. Man does become hypersensitive to these simpler substances; but it appears quite impossible to produce anaphylaxis in animals with them. Landsteiner (39) has, however, shown experimentally that simple substances can become combined with proteins to form new immunological compounds. Thus the reaction to simple chemicals can be brought into line with the reaction to more complex substances.

Much investigation has been done in an endeavour to discover what particular chemical complex was responsible for the elicitation of a positive skin test, and what particular part of the molecule was most efficacious as a therapeutic agent to produce desensitisation. The net result is that the nature of the particular chemical complex concerned has not been precisely defined but it occurs in combination with a protein, in a relatively large molecule, and is soluble in water or saline. Albumins, globulins, proteoses and alcoholic extracts all contain some active principle which is specifically characteristic of the crude substance. It has been shown that one of the structural units in the albumin and globulin

of horse serum is a carbohydrate complex. It is interesting to note that a soluble specific substance, derived from bacterial extracts, is also of a carbohydrate nature.

At any rate, the chemical problems of experimental anaphylaxis and human hypersensitiveness are very strikingly similar. In fact, the two conditions would appear to differ in degree rather than in any profound way.

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MODE OF SENSITISATION.

In chemically simple substances, entrance into the cell takes place readily by direct diffusion, and the absorption of the substance is rapid and simple. In the case of more complex substances, however, the readiness with which entrance into the cell occurs depends upon the diffusibility of the substance. It is necessary for the cell to split this complex substance into its component parts, which, being of simpler chemical structure, can then be dealt with by the cell, as in the case of the simpler substances. To do this, there must be present antibodies, which first are formed in the cell itself, and then appear in the surrounding medium as the excess

when the cellular concentration has reached a certain point. So far as is known antibodies have no definite structure. Zinsser (40) has said that the formation of antibodies is exclusively an attribute of materials which are practically non-diffusible. So proteins cause antibodies to appear and are therefore antigens.

Circulating antibodies.

Now, if a guinea-pig is artificially sensitised with horse serum, antibodies will develop in its blood. This can be shown by:-

1. the fact that such blood will transfer the sensitive state to a normal guinea-pig; and

2. the fact that if small amounts of antigen and strongly diluted serum be mixed in a test tube, a precipitate will appear. This is known as the Precipitin reaction. Different species of animals, and even different animals of the same species, have been proved to vary in their ability to develop these circulating antibodies. It is well known that some horses will produce diphtheria antitoxin in much larger amounts than others.

Passive anaphylaxis has been described. The important points to note about it are:-

1. the necessity for an incubation period; and

2. the fact that the anaphylactic antibody is still present, even though the previously sensitised animal has been treated repeatedly with horse serum, so that he no longer reacts with anaphylactic symptoms to moderate doses of serum and is desensitised.

In the sensitised animal, these antibodies do not persist indefinitely, because after a certain time it is no longer possible to transfer sensitiveness with the serum. So the antibodies must have disappeared. The state of passive sensitisation in the recipient normal animal only lasts about ten to twenty days, and must depend upon the life of the antibodies. If, however, the animal being passively sensitised is of the same species, the sensitisation lasts much longer. The so-called incubation period of passive anaphylaxis is really the time required for the antibodies to pass from the serum into the cells of the injected animal. Such an interval indicates that no reaction can occur until these antibodies become attached to the cells. So that cellular antibodies, as opposed to circulating antibodies, must play a vital part. Zinsser concludes

that passive sensitisation may be accomplished with any serum that contains antibodies, and that the power of such a serum to convey sensitisation is in direct proportion to its antibody concentration. It is difficult to reconcile this in the white rat, which is notoriously resistant to anaphylaxis, except that it may depend upon a different type of immunological process.

In human serum disease, antibodies are demonstrable only when the disease has run its course and they disappear from the blood in a relatively short time. It is to be specially noted that a skin reaction to horse serum appears at the same time as do the serum antibodies, but that it remains positive long after these have gone. Also, the quantity of antibody appears to depend upon the intensity of the serum disease. So that the failure to demonstrate circulating antibodies in asthma and hay-fever patients may be because the individual's resistance has not been of sufficient strength to bring out reacting bodies in such quantities as to be recognisable in the circulating blood.

In human hypersensitiveness, apart from serum diseases, disappointing results have been

obtained in trying to prove the presence of circulating antibodies.

One of the most important discoveries in this whole subject was made in 1921. The serum of Kustner, who was sensitive to fish, was introduced into the skin of Prausnitz, and it was then found by intradermal tests that the skin of Prausnitz had become locally and passively sensitised to fish at the injected site. A lot of work has since been done on this subject by Coca (41) and others. And a new word - reagin - was coined to represent the substance in the sera responsible for this transfer. In other words, Coca claimed that reagins differed in some respects from precipitins. This is true to a certain extent, as a comparison will show:-

1. Heating of reagin - containing serum to 56°C for thirty minutes causes a slight loss of the transferring power -

   Precipitins are not affected by this amount of heat.

2. Reagin - containing serum does not stand keeping on the ice for very long -

   Precipitins keep well.

Coca, however, maintained that reagins were

typical of allergy, and did not occur in non-allergic individuals. This has been shown not to be the case. And in fact they are merely another expression of the reaction to foreign substances. One thing Coca has definitely shown is that reagins and skin tests go hand in hand; and he also states that the reagin content of the patient's serum does not alter during treatment. If this is so, it directly antagonizes one of the conceptions of desensitisation, which is, that treatment tends to exhaust the circulating bodies.

In another respect, reagins and skin tests are very much alike; they appear to persist indefinitely in the circulating blood. In contrast to this, other circulating antibodies disappear after a time.

So that Coca's contention would seem to have a great deal of support, in spite of Zinsser's original conception of a unity of antibodies.

The more recent work of Clark and Gallagher (42) throws, however, some doubt on the idea that reagins persist indefinitely. Their study of individuals, who had previously had horse serum, shows that reagins may in some way be responsible for the manifestations of allergy.

Cellular Antibodies.

That antibodies most certainly exist in the cells can be shown in the following ways:-

1. Dale Reaction.

Dale sensitised guinea-pigs to various antigens, then removed their uteri, thoroughly washed and perfused them to remove all traces of blood, and suspended them in baths of Ringer's Solution. He then showed that if minute traces of the substance to which the guinea-pig was sensitised were now added to the Ringer's Solution, an immediate contraction occurred.

This reaction is undoubtedly due to the presence in the cells of the uterine muscle of specific antibodies; and it provides the most important support for the cellular theory of anaphylaxis. It is the typical method demonstrating that cells contain antibodies and are capable of reacting to direct contact with antigen and without assistance from any circulating antibodies.

2. Manwaring's (45) transfusion experiment.

If a sensitive animal is bled, and reinfused with the blood of a normal animal until there has been an almost complete replacement of blood, the sensitive animal still remains sensitive. This experiment was done with dogs. Another was done

with guinea-pigs, in which the lungs were washed free of blood via the pulmonary artery with Locke's fluid; the addition of goats serum to the perfusing gluid produced remarkable changes in the lungs of the guinea-pig previously sensitised to goat serum; these lungs became fixed, partially expanded and failed to collapse.

Moreover, skin tests in animals must depend on cellular antibodies. In man, a display of hypersensitiveness to some particular substance practically implies that he will give a positive skin test to that substance. The skin reaction must depend upon antibodies attached to the skin cells, for all these cells are capable of reacting when the specific substance is applied. It must not, however, be overlooked that in some hypersensitive individuals, it may not be possible to obtain a positive skin test. And also a positive skin test may be obtained in an individual who is not hypersensitive. In the case of serum disease, persistence of skin reactions, like the persistence of the Von Pirquet tuberculin test, frequently represents the past history rather than the present illness. The size of the skin reaction bears only a crude relation ot the degree of sensitiveness.

In conclusion, it may be said that antibodies fixed to the cells are important in all forms of anaphylaxis and allergy. They are responsible for the reaction which takes place when antigen comes into contact with the cells, and the intensity of this reaction is dependent upon the quality and concentration of the cellular antibodies.

Circulating antibodies, at least precipitins and anaphylactins, represent the excess of those antibodies formed in and by the cells, which is thrown off into the blood stream early in the process of sensitisation. They are concerned with the development of sensitiveness and depend upon the early and excessive reaction of the body towards the antigen. Once this violent early reaction is over and the animal has recovered, these circulating antibodies usually disappear slowly. Other and probably related antibodies (reagins), which develop at the same time, do not disappear from the circulating blood, but persist, like the skin tests, as evidence of the original sensitising process.

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DESENSITISATION.

A consideration of desensitisation will certainly be very helpful in supporting these ideas of the way in which sensitisation occurs.

If a guinea-pig be given a sublethal dose of foreign serum, be allowed to recover from any symptoms thereby produced, and then be given a much larger dose of the same serum, it will be found that no untoward results occur. And by appropriate treatment he may be made refractory to many times the dose which was fatal before this treatment. Weil (44) first used the term "desensitisation" because it seemed to him that the effect of such treatment was on the antibodies of the animal.

There are at least three possible explanations of desensitisation. These will be considered in turn.

First - the antibodies in the blood and in the cells, produced by the first injection, may be exhausted or even destroyed. If such be the case, the protein of the second dose must unite with the antibodies of the sensitised animal, and in this way exhaust their power of uniting with any more doses of the same protein. Weil has shown that small doses of antigen cause a prolonged

incubation period, because the resulting antibody production is slow and poor; larger sensitising doses cause rapid and considerable antibody formations, with a short incubation period. The age and size of the animal seem also to cause variations in the degree of sensitiveness.

The state of desensitisation thus produced is only temporary. Sensitiveness returns slowly, evidently depending upon reconstruction of the antibodies. Dale has shown that desensitisation can be carried out in isolated tissues, in vitro. Obviously, the cellular nature of the antibody must always be an important feature. In spite of the importance of cellular antibodies, however, circulating antibodies modify any reaction that results. Weil found that both actively and passively sensitised guinea-pigs could be protected by injecting considerable amounts of immune serum into their circulation just before inoculation with the second dose. So he concluded that the subsequent injection of antigen united with the circulating antibodies and did not reach the cells. He has, however, also shown (45) that the antigen is attracted more strongly to the cellular antibody than to the circulating antibody.

Furthermore, the fact that the blood of desensitised animals can still transfer passive anaphylaxis to a normal animal shows the presence and persistence of antibodies in its circulating blood, at a time when the injected antigen has already become attached to the fixed cellular antibodies.

It would seem that in the desensitised animal the antibodies are saturated, whereas in the normal animal they do not exist except in small amounts.

Secondly, desensitisation has been explained as a state in which there is a prevention of the union between antigens and antibodies. Antigen and antibody may certainly co-exist in the serum, as may be proved by:-

1. the fact that such a serum will precipitate when antigen is added, thus showing its antibody contents; and by,

2. the fact that such a serum may be precipitated by immune serum from another animal, thus showing its antigen content.

The factor holding antigen and antibody apart is unknown. Such a state is seen typically in human serum disease. It has been recently suggested by Zinsser (46) that this holding

apart of antigen and antibody is due to some colloidal action of the serum, because alterations in the hydrogen-ion concentration or in the electrolyte content can bring about changes in the relations between antigen and antibody. Thirdly, desensitisation is suggested as a condition which is due to the prevention of the reaction toward the hypothetical toxic substance caused by the antigen-antibody reaction. The most obvious factor concerned in such a case would be a drug. Ether and atropine certainly modify, and may even prevent, anaphylactic shock. Sodium chloride has been a subject of much investigation, because it will modify anaphylaxis in dogs. There are two ideas as to how it does this, (a) that the body cells are so saturated by the salt that they become less permeable to the anaphylactic poison; and (b) that hypertonic saline reduces the severity of the anaphylactic manifestations by diminishing the irritability of smooth muscle. In anaphylaxis there is a marked reduction of the carbon-dioxide capacity of the serum - in other words, there is acidosis. It is conceivable that alkalis may modify such an acidosis; and yet, such an acidosis would appear to be more a symptom than a cause of the

of the anaphylactic phenomenon.

The question of colloidal equilibrium has been investigated by French authors (47). They suggest that in shock such an equilibrium is disturbed, and a condition they call "colloidoclassie" results. This is characterised clinically by the following:-

1. the coagulation time of blood is prolonged;
2. the systemic blood pressure falls;
3. the total leucocytes fall to three to five thousand per cubic millimetre;

On the other hand, the experience of Dale(48) led him to maintain that the surface tension or viscosity of the serum was not affected when such serum was incubated in the presence of starch. So that the importance of colloids would appear to be negligible.

In man, the problem of desensitisation presents many difficulties. A case of serum disease is more sensitive than normal after recovery from recent serum disease, and is thus not desensitised. In the course of time, however, such an individual will return to his original state of sensitiveness, although the skin reaction to the original serum may persist indefinitely. In the case of an allergic person, this is not the case.

Prophylactic treatment of hay-fever cases gives satisfactory clinical results in about seventy per cent of cases, in certain individual pollen types. And yet the clinical success is not accompanied by any uniform dimunition in the size of the skin test. Nor is greater improvement derived from the use of larger doses of pollen. So there is difficulty in attributing any results obtained to a desensitisation with exhaustion of antibodies. On the other hand, it has been shown by Mackenzie (49) that repeated local injections of an antigen can cause the skin reaction of hay-fever patients to be diminished or obliterated, and that this is specific for the particular substance. Surely such a result must include some mechanism concerning the presence of antibodies.

Clinical observation would seem to support the theory of antibodies and desensitisation by their exhaustion.

Another point of interest is the occurrence in hypersensitive patients of general reactions of some severity following specific treatment, such as in hay-fever. Too large a dose of pollen extract has been known to give rise to urticaria, hay-fever, asthma and collapse. The remarkable finding in

such a case is that desensitisation has not resulted, after recovery from the general reaction. So that it is difficult to see how desensitisation occurs in any ordinary sense in human allergy.

Bacterial Allergy.

In the discussion of sensitisation, no reference has so far been made to a very important subject, namely, Bacterial Allergy. Hypersensitiveness to epidermals, foods or dusts is a relatively straight forward problem with clear cut methods of diagnosis, as well as of treatment. It is, however, quite common to encounter cases, displaying allergic phenomena, following some infective process within the body. Such cases form a typical group, which has certain characteristics:-

1. the attacks are usually of short duration and limited course, in many cases confined to one season of the year;
2. they are of comparatively mild nature;
3. there is a rapid onset of allergic reaction within a day or two;
4. they are preceded by mild infections such as catarrhal conditions of the upper respiratory tract;

5. They differ from severe infections with high fever and acute symptoms, during which asthmatic and other allergic manifestations are generally not seen.

So it will be shown that the same manifestations which result from the entry from without of foreign protein substances into the body, can be produced by causes within the body. All the same, it does not seem possible that the mechanism of the two conditions is the same. One of the foremost stumbling blocks is undoubtedly the behaviour of the skin test. An immediate urticarial reaction follows a skin test with the ordinary simple protein extracts. With the application of bacterial products to the skin, however, the characteristic result is a delayed reaction of inflammatory nature, requiring about twenty four hours to be fulfilled. That is to say, the nature of the reaction and the time of its materialisation are quite different.

There is another obvious stumbling block. Treatment with vaccines very rarely results in the production of a general reaction, such as urticaria and coryza.

A lot of experimental work on animals has

been done in this subject. It would seem that all the analogies with serum and protein anaphylaxis have been fulfilled with bacterial materials.

As stated above, the skin reaction to bacterial products is different from that to simple protein extracts. It would appear to represent the crux of the whole problem. The first observation of any kind on this subject was that of Jenner in 1798, when using cow pox virus. Nearly a hundred years later Koch described the tuberculin reaction, which he demonstrated as occurring in animals with active tuberculosis. This subject was placed on a sounder basis by Baldwin (50), who showed that there were two types of reaction;-

(a) a reaction of the whole animal, quite like the reaction of protein anaphylaxis; and

(b) a local inflammation, appearing slowly and only in animals with active infectious disease.

He was of opinion that some product is set free by the disintegration of bacilli and is carried in the blood to distant cells to make them locally sensitive to tuberculin.

The relationship between the skin tests to bacterial products and the part which they might

represent in the hypersensitiveness of the animal were thoroughly investigated by Zinsser (51). He infected a guinea-pig with tuberculosis and noted that the skin test first became positive in about ten days; also when the animal was killed and the uterus suspended in Ringer's solution - as in the Dale method - the addition of tuberculin to the solution caused the uterus to contract, after the infection had lasted three weeks. Next, a guinea-pig was treated with dead bacterial products. Then he observed that in this guinea-pig, a positive skin test to tuberculin was but rarely obtained, but that the above described uterine reaction was quite frequently seen. Thinking that there might be different elements producing the skin reaction and the uterine reaction, Zinsser endeavoured to split the bacterial bodies by chemical means. Two substances were thus obtained - the "nucleo-protein" (a precipitate) and the "proteose residue" (a filtrate). These two substances can produce a variety of reactions in prepared animals. The nucleo-protein differs from the residue in that it is antigenic, and it can stimulate antibody production in cells and serum. In 1923, Avery and Heidelberger (52) obtained a substance from massive cultures of

pneumococci which they called "soluble specific substance", and which is analagous with the proteose-residue of Zinsser. These two workers found that this soluble specific substance was built up of glucose molecules and is in fact a polysaccharide. Zinsser had shown that his residue was free from protein. It is very interesting to note that further work by Avery, along with Goebel and Tillett (53), confirms the theory that specificity depends upon the carbohydrate radical in chemical structure. As stated, Avery's carbohydrate and Zinnser's residue are quite the same. This specific carbohydrate reacts with all immune sera with extreme delicacy, and will elicit an immediate reaction with wheal and erythema when injected in high dilution into the skin of sensitised animals, and also in man. On the other hand, this specific substance cannot induce the formation of antibodies in the cells or serum.

So in bacterial allergy, there appear to be two types of reaction. The <u>first</u> is akin to protein anaphylaxis; and it is possible to correlate bacterial anaphylaxis with protein anaphylaxis on the following grounds:-

1. an animal can become sensitive to soluble bacterial products - nucleo proteins, which are split off from the bacteria in the local lesions;

this may be demonstrated by anaphylaxis of the whole animal or by the reaction of an isolated smooth muscle;

2. Passive anaphylaxis can be effected with the animal's serum in a normal animal;

3. Skin tests of the immediate type, elicited with the purified bacterial carbohydrate, can be readily obtained in guinea-pigs sensitised with these bacterial products.

The second type of reaction is quite distinct. It is peculiar to bacterial hypersensitiveness, and is not found in non-bacterial protein anaphylaxis. The essential part of this reaction is that it must involve injury to the tissues of the animal to produce pathological lesions of definite extent. It is characterised by a change in the animal so that the application of bacterial products, like tuberculin, to the skin will produce a delayed reaction which is inflammatory and not oedematous in nature; and it may occur within a week of treatment. The tissue injury must involve the introduction into the animal body, as a whole, of substances which can sensitise the cells in a special way. These substances have been designated the "third substance". It is the production of the late skin test which differentiates this type of

reaction from the first. This skin reaction results from pathological changes which may be caused by active infections or by large enough doses of non-living bacterial products, provided these products still contain remnants of formed bacterial bodies. It is essential for local tissue reactions to be produced.

If guinea-pigs are sensitised with the tubercle bacillus, the anaphylactic shock produced by the specific carbohydrate does not appear to prevent or diminish the cutaneous reaction to old tuberculin in those animals which recover. The immediate skin reaction to the pneumococcus carbohydrate has been shown by Tillett (54) to occur at the time of recovery. But the delayed reaction to the so-called nucleo-protein of the pneumococcus was present both before and after the time of recovery and was not related to the concentration of circulating antibodies. In all experiments where intracutaneous injections are used, the injected mass must be held in situ for a time, so that local reactions of some extent must result. And yet animals thus treated are not highly immune. Moreover, the immunity, as shown by circulating antibodies or resistance to infection, does not appear to correspond with the result of the skin test.

So that this tuberculin type of reaction is definitely different from immunity as shown by the presence of circulating antibodies and resistance to infection.

In summary, the carbohydrate substance merely determines the specificity of the immediate anaphylactic or allergic reaction and has no antigenic properties. The delayed inflammatory reaction is obtained with whole bacteria or their nucleo-protein fraction. And in sensitiveness of this inflammatory type passive transfer through the serum is not possible.

The study of bacterial allergy in man received rather a set-back after the first few observations because there did not appear to be any relation between the presence of skin tests and the presence of circulating antibodies. It was observed in asthmatic patients treated with vaccines that the beneficial results obtained bore no constant relation to the dimunition of the skin test. It is known that circulating antibodies of all types tend to disappear fairly rapidly from the blood stream.

In any infectious disease in man, the presence of an inflammatory process is helpful in understanding how delayed inflammatory skin reactions

are easily elicited with the products of the corresponding organism. It is also known that young children are insensitive to skin tests with bacterial products. In the case of a toxin, like diphtheria, a positive reaction to a skin test means a lack of circulating antibodies; but in other instances, it is found in patients (a) recently recovered from the disease concerned, or (b) in those harbouring a persistent focus of disease.

In chronic diseases, many interesting facts have been brought to light. Swift (55) and his co-workers have suggested that the joint manifestations of arthritis are specific allergic responses. By using agar foci and keeping up a chronic infection with non-haemolytic streptococci, they caused rabbits to develop symptoms quite comparable to arthritis in man; and they showed that such could be produced by any organism with which a focus of infection could be established.

Swift actually states that "it is the state of the patient rather than the presence of a particular germ which causes the rheumatism". And Poynton and Schlesinger (56) would seem to corroborate this. They suggest that arthritis, relapses following tonsillitis, and fleeting

pains are allergic in nature and due to a sensitisation to the products of disintegration of the living bacteria. These considerations follow much clinical and experimental evidence, in which the varied results of the skin reactions obtained would appear to depend upon the state of hypersensitiveness to certain products of streptococci rather than upon a specificity of any one type of streptococcus. Therefore in asthma it seems logical to regard many of the patients as being sensitised by a substance in bacterial origin, arising from some focus of active disease.

Bacterial skin tests of delayed inflammatory type represent the remains of active infections that have past. They do not appear to be in any way related to concurrent disease.

Desensitisation in bacterial allergy is a subject of vast importance, about which not a great deal is known. Desensitisation in an anaphylactic sense would not appear to be all that is necessary. Rackeman (57) has shown that successful vaccine treatment of bacterial asthma only occurs in those cases in which definite local reactions are produced to therapeutic doses. This fact, as well as the well-known relief often to be

obtained in certain cases of asthma, urticaria, and hay-fever by the use of such substances as milk and peptone, would appear to show that this local reaction is of great importance. Another important observation is whether desensitisation is better achieved by intra-cutaneous injections with the deliberate object of producing large local reactions. In such a case, the question will arise of the effect of the inflammatory reaction in general in releasing such a substance as histamine. Also, it must not be forgotten that vaccines can produce circulating antibodies in animals and in man. Granted that this is a specific process, the specific immunizing effect can still be obtained by non-specific means. So that many methods of treatment which are considered non-specific may in fact ultimately produce specific effects. In using non-specific vaccines, symptomatic relief has often appeared to be greater from the first few doses than from subsequent ones.

Beyond the fact that the two reactions above discussed are now recognised as separate entities, it would seem that the mechanism of bacterial

hypersensitiveness remains undefined.

By way of comparison, a few remarks would not be out of place. It has been shown that in protein anaphylaxis the antibodies are in the cells in large numbers (?) and that they are similar to those in the serum; but that it is their location and concentration which determine the sudden reaction. In Bacterial Allergy, the antibodies are similarly in the cells, but are of a more special kind; it is the activity of the infectious process which causes them to appear; so that they must depend upon a "third" substance. Attached to the cells of the skin and perhaps to the cells of other organs, they prepare for an inflammatory, destructive lesion when contact occurs with the protein-containing product of the specific substance,

And finally, a clinico-pathological contrast will be found illuminating. In non-bacterial sensitisation, the local blood vessels dilate rapidly, their walls become permeable, and an exudation quickly occurs; and there is little or no destruction or new formation of tissue. In bacterial sensitisation, on the other hand, the reaction is most marked in the tissues wherein lie

the organisms; the exudation generally persists for weeks or months; and destruction and new formation of tissue both occur. Pottenger (58) makes a very interesting comparison, perhaps even diagnostic, as follows:-

Non-bacterial Allergy.	Bacterial Allergy.
Bronchospasm.	Fever.
Increased bronchial secretion.	Sweating.
Increased permeability of blood-vessels and cells.	Contraction of the pilomotor muscles.
Increased potassium-calcium ratio.	Rapid heart.
Increased alkalinity of the tissues.	Poor appetite.
Eosinophilia.	Constipation.
	Decrease in the alkalinity of the blood.
	Leucocytosis.
	Anaemia.

From this comparison, he concludes that non-bacterial allergy is expressed as a parasympathetic or vagus syndrome, and that bacterial allergy is expressed as one of the sympathetic system.

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SPASMODIC BRONCHIAL ASTHMA AND ANAPHYLAXIS.

There is substantial evidence to uphold the idea that spasmodic bronchial asthma is a manifestation of anaphylaxis in a sensitive subject. This contention was first put forward by Meltzer (59) in 1910. He pointed out that the then so-called nervous asthma was due to a stenosis of the bronchi, and that anaphylactic shock was due to the same condition. He thereupon offered the theory that "asthmatics are individuals who are sensitised to a specific substance and that the attack of asthma sets in whenever they are intoxicated by that substance".

First, the symptoms of anaphylactic shock in animals must be considered. The reaction in the guinea-pig is so typical that it will be described in detail. The experiments are usually done with horse serum. Shortly after a sensitised guinea-pig has been given the second dose of the specific antigen, the animal will stay quiet for a minute or two. Then will ensue the following symptoms, in order:-

1. Roughening of the hair, general tremor and restlessness;

2. scratching of the nose, and passing of urine and faeces;
3. difficulty in breathing, with short, jerky contractions of his chest muscles, which will increase rapidly in severity;
4. cough, as these attempts at breathing become more violent;
5. convulsi ons;
6. death;

This represents acute anaphylactic shock with death in a few minutes. Of course, the animal may recover after having severe symptoms, if he is less highly sensitised, or if the second dose is given in smaller amount, or if it is administered so as to be absorbed with less rapidity.

The post-mortem findings of an animal dead of anaphylactic shock are very characteristic. They are:-

1. acute pulmonary distension, which is most striking; the lungs are distended and pale, and do not collapse; the heart and lungs can even be removed "en bloc", and form a complete cast of the chest cavity;
2. the surfaces of the lungs show pin-point haemorrhages;

3. the cut surface of the lung is pale and smooth;
4. the intestines are often in active peristalsis and may show petechiae on the peritoneal surface;
5. the blood is still fluid, and
6. there is congestion of all the organs.

The physiology of anaphylactic shock was worked out by Auer and Lewis (60). They introduced a cannula into the trachea of a guinea-pig in anaphylactic shock and found it was impossible to inject more air into the bronchi or to draw any air out. So they concluded that the difficulty was that the bronchi were constricted from contractions of the bronchial muscles. Thereupon they cut the vagi on both sides, but found the condition remained. So that the contraction was proved to be due to a direct stimulation of the bronchial muslces. Furthermore they showed that the severe pulmonary emphysema was not a secondary effect of any violent contraction of the diaphragm. Further interesting experiments showed that substances, such as histamine and peptone, produced acute bronchospasm.

In the guinea-pig it is the contraction of smooth muscle which accounts for the characteristic symptoms.

It is important to note that with a less violent reaction, the main symptoms may be an urticarial rash. This starts at the site of inoculation and then spreads all over the body. From a consideration of the above, it is evident that the anaphylactic poison produces two distinct processes.

(a) a spastic contraction of the bronchial muscles;

(b) capillary disturbance, resulting in dilatation of the superficial minute vessels, a contraction of the larger arterioles and an increase in capillary permeability.

Of course, typical anaphylaxis as described must be rare, because of the widespread use of sera therapeutically without ill-effects. It is far commoner to observe serum disease, following the use of such sera. This occurs in normal individuals who have never had foreign serum before, or in those who have had such serum many years previously. Its main characteristics are urticaria, joint pains, slight fever and malaise, occurring seven to ten days after the dose of serum. It usually follows a large dose of serum. There is much discomfort to the patient and it may be very alarming, but it is rarely fatal.

So then the symptoms of anaphylactic shock may vary widely in different animals. Anatomical

and physiological differences must account for this diversity, of which the chief is the varied distribution of non-striated muscle in the different species.

The phenomena of anaphylaxis having thus been described in detail, it becomes easier to assemble the evidence in favour of spasmodic bronchial asthma being a manifestation of anaphylaxis in a sensitive subject.

First, it has been shown that anaphylactic shock occurs in an animal that has previously been sensitised. That is, there must be deliberate treatment of the animal with the specific substance, consisting in the parenteral introduction of a small dose of the protein. In asthma, hypersensitiveness develops slowly and insidiously, and frequently follows prolonged and repeated contact with the particular substance. So that whereas the mode of sensitisation varies somewhat, the resulting condition of hypersensitiveness is essentially similar. In other words, the foundation is strikingly comparable.

Secondly, the symptoms present a characteristic similarity in the development of difficulty in breathing, which is definitely obstructive in type.

And this is accompanied in each case by a fall in blood pressure.

Thirdly, in the consideration of pathology it will be noted that marked similarity also exists. The striking thing about the anaphylactic animal is the marked pulmonary distension. In asthma, the lungs in general and the alveoli in particular are distended during the attack - air is retained in them. In both cases, this pulmonary distension can be accounted for by the contraction of the smooth muscle of the bronchi.

Fourthly, as said before, the anaphylactic poison causes (a) a spastic contraction of the bronchial muscles and (b) capillary disturbance. Now, in 1917, Eppinger and Hess (63) described in detail a condition they termed "vagotonia", with the following characteristic:-

1. bronchial spasm;
2. contracted pupils;
3. slow pulse rate, varying with excitement;
4. gastro-intestinal hypermotility;
5. tendency to flushing;
6. irritability of the skin - dermagraphia;
7; eosinophilia.

So it is interesting to note that vagotonic patients show many of the characteristics of

asthmatic subjects, and at the same time to realise that the anaphylactic poison produces very similar symptoms and clinical signs.

And so, if the idea that prolonged contact leads to an actual acquisition of hypersensitiveness is accepted, it is possible to interpret the asthmatic phenomena as true anaphylaxis.

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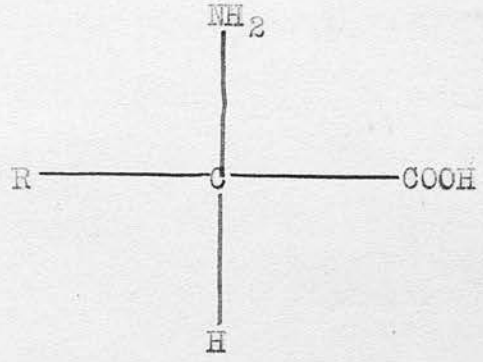
BIOCHEMISTRY OF THE AMINO-ACIDS.

Up to the present twenty amino-acids have been obtained by various complex procedures and definitely identified. They are essentially both substituted ammonias and carboxyl acids, and most of them have the type formula



In virtue of this double property of being at the same time base and acid the amino-acids are all amphoteric, reacting as bases with acids, and as acids with bases.

Moreover, the amino-acids ionize very slightly in solution in two ways. The simplest of the group is glycerine. Its behaviour may be taken as typical:-

1. $NH_2 . CH_2 . COOH \rightarrow NH_2 . CH_2 . COO^- + H^+$

2. $COOH . CH_2 . NH_2 + HOH \rightarrow \begin{matrix} COOH & CH_2 & NH_3OH \\ \rightarrow COOH & CH_2 & NH_3^+ + OH^- \end{matrix}$

The second series of changes parallels the formation of ammonium ions -

$$NH_3 + HOH \longrightarrow NH_4 OH \longrightarrow NH_4^+ + OH^-$$

The extent to which these two different types of ionisation takes place respectively depends upon the pH of the solution. If the reaction be alkaline, then the first is the main change; and from such

solutions alkaline salts of the amino-acids will crystallise. If the reactions be acid, then the second type of ionisation predominates, and from such solutions acid salts will crystallise, such as glycine hydrochloride. At some intermediate point, known as the isoelectric point, ionisation is reduced to a minimum.

Derivation.

Glycine -	$C_2H_5NO_2$ -	derived from proteins such as gelatin and elastin.
Alanine -	$C_3H_7NO_2$ -	derived from proteins such as keratin (horn) and fibroin (silk).
Serine -	$C_3H_7NO_3$ -	present in small amounts in the hydrolysed products from many proteins.
Cysteine -	$C_3H_7NSO_2$ -	present free in many tissue cells.
Cystine -	$C_6H_{12}N_2S_2O_4$ -	may be considered as responsible for most of the sulphur present in protein compounds.
Methionine-	$C_5H_{11}SNO_2$ -	derived from casein, egg albumin, yeast and wool.
Valine -	$C_5H_{11}NO_2$ -	derived from caseinogen.
Leucine -	$C_6H_{13}NO_2$ -	one of the amino-acids most easily liberated from the protein molecule.
Aspartic Acid -	$C_4H_7NO_4$ -	widely distributed in plants.
Glutamic Acid. -	$C_5H_9NO_4$ -	one of the chief products of hydrolysed proteins.

Tyrosine	- $C_9H_{11}NO_3$	- yielded by hydrolysis of most animal proteins.
Histidine	- $C_6H_9N_3O_2$	by hydrolysis from the protein molecule.
Arginine	- $C_6H_{14}N_4O_2$	
Tryptophane	- $C_{11}H_{12}N_2O_2$	
Proline	- $C_5H_9NO_2$	
Lysine	- $C_6H_{14}N_2O_2$	
Hydroxy-proline	- $C_5H_9NO_3$	
Hydroxy-glutamic acid	- $C_5H_9NO_5$	
Isoleucine	- $C_6H_{13}NO_2$	
Phenylalanine	- $C_9H_{11}NO_2$	

Many of these amino-acids exhibit different optical properties in acid and in alkaline solutions, and their activities sometimes vary according to the degree of acidity or of alkalinity. The majority of them are laevo-rotatory.

Since the amino-acids are at the same time acids and derived ammonias, two molecules of the same or of different acids should be able to unite and form a di-peptide, as for example:-

$$\underset{\text{Glycine}}{NH_2.CH_2.COOH} + \underset{\text{Glycine}}{HNH.CH_2.COOH} =$$

$$\underset{\text{Glycyl-glycine.}}{NH_2.CH_2.CO.NH.CH_2.COOH} + HOH$$

and generally:-

$$\underset{\text{Any amino-acid}}{R.CHNH_2.COOH} + \underset{\text{Any amino acid}}{HNH.CHR'.COOH} =$$

$$\underset{\text{Any di-peptide.}}{R.CH_2NH_2.CO.NH.CHR'.COOH} + HOH$$

These dipeptides will also be amphoteric; they also contain amino and carboxyl groups, and so should also unite with amino-acids to form still more complex compounds, tri-peptides:-

$CH_3.CHNH_2.CO.NH.CH_2.COOH + HNH.CH(CH_3).COOH$
alanyl-glycine + alanine

$=$

$CH_3.CHNH_2.CO.NH.CH_2.CO.NH.CH(CH_3).COOH + HOH$
alanyl-glycylaline

The importance of these synthetic polypeptides lies in their similarity to the proteins, and their partially broken down products, the proteoses and peptones.

These polypeptides give typical protein colour reactions only when they contain the amino-acid radicals to which these are respectively due. These colour reactions are brought out by the Buiret Reaction, Millon's Reaction, Xanthoproteic Reaction and the Glyoxylic Acid Reaction.

When hydrolysed, polypeptides break down to amino-acids; and many of them are broken down in this way by the various proteoses, the enzymes which normally act on proteins.

These facts strongly suggest that the ordinary protein molecule consists of a long chain of amino-acid radicals joined through a long series of peptide linkages. Other types of linkage must,

however, undoubtedly occur. The pepsin of the gastric juice will not decompose the synthetic polypeptides, and cannot therefore act on the peptide linkage as it exists in these compounds. It acts immediately on proteins to break them down to proteoses and peptones, setting free in the process at least twenty per cent. of the amino-groups. It is usually concluded that this twenty per cent. is therefore not held in the simple peptide linkage. It has recently been shown that during peptic digestion equivalent amounts of - NH_2 and - COOH groups are set free. So that the actual linkage upon which pepsin acts is still undecided.

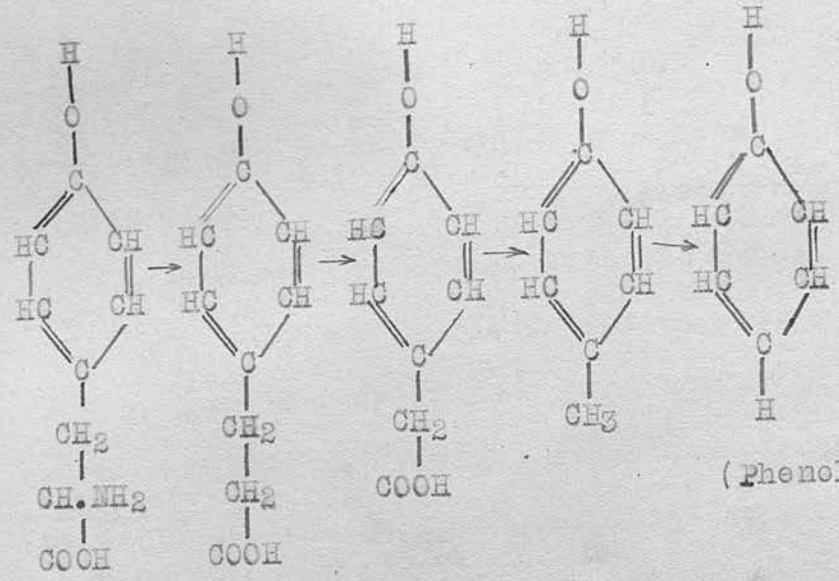
Now in the intestines, bacteria attack protein decomposition products. Their actions on amino-acids are of two distinct types:-

1. they deaminise the acid, with the production of ammonia and a derived fatty acid, and then subsequently split off carbon dioxide from this, leaving derived phenols; or

2. they split off carbon dioxide at once, producing a more toxic amine.

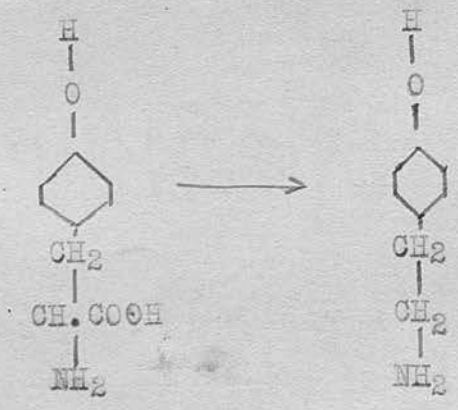
These actions can be illustrated with tyrosine.-

(1)



(Tyrosine) (Phenol)

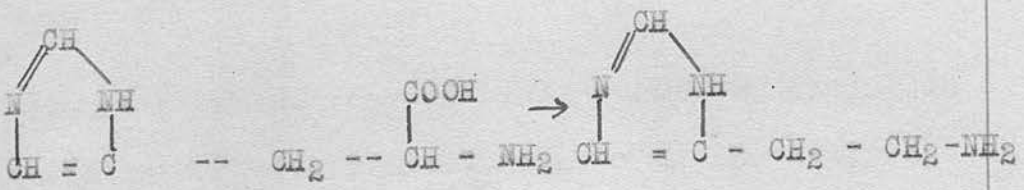
(2)



(Tyrosine) (Tyramine)

By the first method, phenol is eventually produced; by the second, tyramine is formed.

With tryptophane, skatole and indole are formed by the first method, and the second results in the production of tryptamine. By this second type of reaction, alanine gives rise to ethylamine, argmine to agmatine and histidine to the important compound histamine (β - iminazolylethylamine).



(Histidine) (Histamine)

It is to be borne in mind that bacterial actions that can occur in the intestine are not limited to the final hydrolysed products of proteins. It has been shown that various streptococci can act on proteoses and peptones, and that B. coli can decompose caseninogen.

The amines, acids and phenols formed by bacterial action are all absorbable through the intestinal wall; and some of them, or their derivatives, are usually present in urine.

The ease with which these products can be absorbed suggests that they can be responsible for certain symptoms of toxicity in the organism. The compounds so absorbed are, however, largely rendered innocuous by chemical changes to them produced in the liver, before they can reach the general circulation, provided their concentration is small. If the toxic compounds are produced in concentration greater than the liver can cope with, it seems possible that they may then produce their pharmacological effects.

Many of the amines, from ethylamine up to tyramine, when injected into the blood stream,

produce a marked rise of blood pressure, acting as constrictors of the smooth muscle of the arterioles. On the other hand, when histamine is injected into a vein, the blood pressure falls, while there is an accompanying rise of body temperature and bronchial spasm; so it stimulates smooth muscle.

Phenol, and its precursor, para-cresol, are not very toxic, and the liver has no difficulty in excreting them as conjugated sulphates (thus they form part of the ethereal sulphates in the urine). The odour of healthy faeces is due in large part to indole and skatole. The liver oxidises indole, and the product, indican, is excreted in the urine.

It seems very probable that bacteria acting on polypeptides of varying complexity can produce compounds of great toxicity. It has recently been shown by Kendall (64) that the chemical action of any bacterium depends in great measure on the medium in which it exists, and that, provided this medium contains a sufficient proportion of carbohydrate, the products of the action are non-toxic. Such an observation obviously has important practical applications.

METABOLISM OF PROTEINS IN THE BODY.

Proteins do not undergo any digestion in the mouth. The first stage of their digestion occurs in the stomach. The hydrochloric acid and pepsin of the gastric juice act upon the proteins and convert them through the stages of acid metaprotein and primary and seceondary proteoses into peptones. Rennin converts caseinogen into soluble casein; and in the presence of calcium salts, this casein is precipitated as insoluble calcium caseinate, and is subsequently digested to the peptone stage. Nucleo-proteins lose a molecule of protein and nuclein is left.

The next seat of digestion is in the duodenum. Here there is an alkaline medium in which the trypsin of the pancreatic juice rapidly breaks down protein to alkali metaprotein, proteoses, peptone, polypeptides and may even liberate some amino-acids, such as tryosine and leucine. The presene of the bile-salts greatly facilitates this process of digestion. Nuclein loses another molecule of protein and nucleic acid is formed.

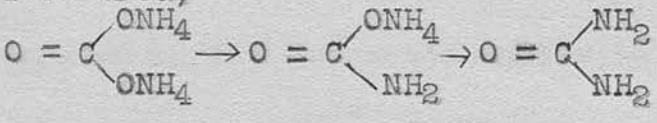
In the small intestine, further on, the erepsin of the succus enterious completes the breakdown of polypeptides into amino-acids, a process which

goes on partly in the lumen and partly in the wall of the intestine. It would seem that nucleic acid is acted upon by a series of ferments which are present in the lumen or can be extracted from the mucosa of the small intestine. First, it is split up into four mononucleotides, compounds which have as a formula "H_3PO_4 - carbohydrate-base". The H_3PO_4 is then split off, leaving combinations of sugar and base called nucleosides. There are two pyrimidine and two purine nucleosides. The two former undergo no further disintegration; but the two purine nucleosides are further split up into the carbohydrate and purine bases, adenine and guanine.

So the amino-acids form the end products of protein digestion. They are absorbed from the intestine and pass via the portal radicles into the liver. Here one of two processes awaits them. Some pass through the liver into the systemic circulation, and so on to the tissues where they are used to make up for the wear and tear which occurs during activity. The rest undergo a process known as deamination, in the liver, in which ammonia is liberated and converted into urea, and a non-nitrogenous residue is left. This process of deamination is a very important one. The

nitrogenous fraction of the amino-acid is thrown off, so that the valuable non-nitrogenous portion may be subsequently utilized. Such a process is probably accelerated in the body by an enzyme. The ketonic aldehydes which result may be hydrolysed, oxidised or reduced. Probably, the process of deamination is reversible; that is, given the appropriate fatty acid grouping, the liver can take up ammonia and re-form amino-acids.

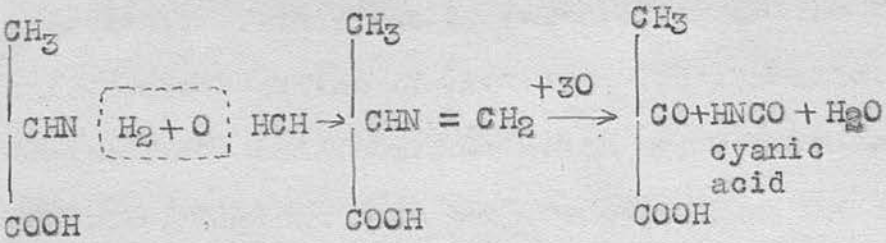
As to the fate of the ammonia, there is some difference of opinion. The orthodox view is that it unites mainly or entirely with carbonic acid to form ammonium carbonate, which is dehydrated to form urea;



(ammonium carbonate) (Ammonium carbamate). (urea)

Fearon is, however, of opinion that the amino-acids combine temporarily with andehydes; a compound is thus formed which is oxidised to form a ketonic acid and cyanic acid; the latter is hydrolysed to form carbon dioxide and ammonia; and the ammonia formed unites with more cyanic acid to form urea.

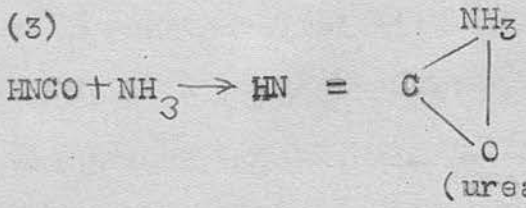
(1)



(2)

$$HCNO + H_2O \longrightarrow CO_2 + NH_3$$

(3)



The fate of the individual amino-acids is as follows:-

Glycine)
Analine) are converted wholly into glucose.
Cystein)

Aspartic acid)
Glutamic acid) are converted partly into glucose.
Arginine)
Proline)

Leucine) Yield acetone bodies.
Tyrosine)

Histidine) Yield neither sugar nor acetone bodies.
Tryptophane)

Glycine - is used in the formation of bile-salts.

Now certain amino-acids are essential for normal health and growth and must be provided in the protein of the food. Such are tryptophane, lysine, tyrosine, cystine and histidine.

It is believed that the amino-acids resulting

from protein digestion can stimulate cellular activity. This power is referred to as the "specific dynamic action of protein". It is attributed to the fatty acid residues which are left after the ammonia groupings have been removed from the amino-acids.

The end products of protein metabolism are to be found in the urine. The total nitrogen excretion runs parallel with the protein intake. The chief nitrogenous constituent of the urine is urea, which is thus an index of protein intake. This still holds true in starvation, in which the urea is derived from tissue protein which is being used for energy purposes. Half the uric acid excreted in the urine is also derived from the nitrogenous intake. The other half, and creatinine, are the result of tissue activity.

Some of the aromatic amino-acids, such as tryptophane and tyrosine, pass into the large intestine where they undergo putrefactive changes, and are converted into indol, skatol and phenol. These latter substances are absorbed into the blood, carried to the liver where they are oxidised, and finally excreted in the urine as the ethereal sulphates.

So the protein in the diet is the sole source of the nitrogen and sulpher which are needed for tissue repair. And it gives rise to the amino-acids, which go to form essential secretions and enzymes. Moreover, protein stimulates body metabolism and is a source of energy.

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RELATION OF PROTEINS TO ASTHMA.

It is a reasonable thesis to conclude that the various manifestations of allergy are produced by the action of some poisonous substance of a characteristic and particular nature. Such a poison must arise from the varied reactions which take place when different allergens come into contact with cells, which bear antibodies specific for these allergens, and the poison must be relatively uniform. Such poison produces characteristic effects, which are:-

1. Spasms of smooth muscle;
2. Contractions of small arterioles;
3. Increases in capillary permeability; and
4. Stimulation of glands,

and these give rise to various clinical symptom complexes.

In a previous section, reference was made to Friedberger's theory that the symptoms of anaphylaxis depend upon an anaphylatoxin formed by the contact of antigen and antibody. The substantiation of this theory depended upon the demonstration of the formation of a poison when antigen and antibody were incubated together outside the body.

Vaughan's demonstration of a protein poison,

produced from bacteria by chemical means, supported this theory in that is suggested that similar proteins were contained in other antigens. Then Jobling and Petersen showed that fresh active serum could produce a serotoxin which had a considerable poisonous effect, when acting upon a great variety of substances. This poison was shown to be derived from the serum itself, and the substrate acted merely to withdraw the antiferment and so release the normal serum ferment to act upon the normal serum protein and to split a toxic substance from it.

Symptoms, simulating anaphylaxis, can be produced by the introduction into animals by injection of a number of substances. Among these are peptone and histamine. Now histamine is only one of a group of amines which may be derived from the proteins of the body, either by the action of specific enzymes or by some physico-chemical means. They are divided into two groups by Koessler (96):-

(a) those with a single basic nitrogen group - examples:- isobutyl amine and phenylethyl amine;

(b) those with two basic nitrogen groups - examples:- putrescine, cadaverine, imidazolethylamine (histamine).

Of these two groups, the diamines have received much more attention. It is probable, however, that a

number of clinical conditions depend upon some action of the monamines - such as ptomaine poisoning. And in passing it will not be out of place to draw attention to the symptoms which sometimes follow the injection of typhoid, paratyphoid A and B vaccines, blood transfusions and Salvarsan, made up with distilled water which has been standing some days. These all tend to show that relatively simple substances can act as poisons to produce symptoms which closely simulate anaphylaxis.

The next step forward was made by Hanzlik (97) who pointed out that the anaphylactic symptoms occurring after the injection of protein materials into prepared animals were not very different from similar symptoms occurring in normal animals, when a wide variety of substances were injection intravenously. Such symptoms are:- tremors, sweating, dyspnoea, cough, nausea, vomiting, cyanosis, headache, excitation, collapse, falling blood pressure and even death. Various factors are evidently concerned, in the production of these symptoms. These are:- stimulation of smooth muscle, bronchial constriction, closure or relaxation of veins, alteration in the coagulation time, agglutination of blood platelets with the formation of thrombi,

dimunition in the carbon dioxide, and dilution of the blood. So it is obvious that Hanzlik's observation is reasonable. Now, the incubation period in anaphylaxis is the time necessary for the elaboration of antibodies by which the foreign substance is made diffusible and so destroyed. And the difference between anaphylaxis as such and other anaphylactoid phenomena lies in the diffusibility of the different substances, in the case of their absorption by the cell, and in the need or lack of need of antibodies. So that the nature of the foreign substances is of primary importance, particularly in determining the speed of the reaction.

There is another factor which certainly should not be overlooked. Normally, adrenalin causes no reaction in the bronchi; but if the bronchial muscles are in a state of spasm, it will relax the bronchi. So that it is the condition of the cells and not the drug which is modified. Possibly, there is some alteration in the surface of the cell.

Hanzlik lays great stress on these physico-chemical changes in the cells. Drugs and poisons can act directly on normal cells unprepared for their reception; but sera and proteins require modification of the cell. It would appear that this

modification is highly specific for each protein. So that it cannot be regarded as a characteristic of allergy. It represents merely the production of specific antibodies.

Histamine

The discussion of this protein compound is a subject of great practical and theoretical importance in the consideration of allergic conditions. Histamine has been shown to be derived from histidine, which is found in all the tissues of the body. It possesses a characteristic action.

Histamine in animals.

The result of injecting histamine intravenously into animals is shock, which shows its effect in two ways. These are:-

1. a marked contraction of smooth muscle, as seen in bronchial constriction in guinea-pigs; and
2. a dilatation of all peripheral blood vessels, with a striking fall in blood pressure.

A detailed explanation of the second of these effects is called for. It has been shown to occur in rabbits, dogs, cats and guinea-pigs. Under normal conditions the capillaries open and close, allowing the blood to circulate now through one set of capillaries and now through an adjacent set.

Histamine produces a dilatation of all the capillaries at one and the same time. All the smallest arterioles dilate as well. In fact, as has been truly said, the patient would appear to bleed into his own vessels. In consequence of all this, blood fails to reach the heart in requisite amount and the blood pressure falls.

Histamine in man.

When histamine is injected into man, there is also a fall in peripheral blood pressure and a well-makred dilatation of superficial blood vessels. The face and the skin both flush. The effect, however soon passes off, it being a matter of minutes.

Histamine also has a characteristic result when applied to the skin. A local dilatation of blood vessels occurs, followed promptly by an extravasation of serum from the capillary wall - that is, a wheal is formed. This is seen in animals and in man, and is just like the skin reaction which occurs when the specific substance to which they are sensitive is applied to their skin in susceptible individuals.

As stated before, histidine has been found by Dale and his associates (98) in all the tissues of the body; and histamine can be split off by an oxidising process very easily. Barger and Dale (99)

have shown that histamine could be extracted from the mucous membrane of the intestine.

An observation of great importance was that of Koessler and his co-workers (100), who demonstrated that histamine could be produced by bacterial action. The bacteria were grown in broth which contained histidine. On injecting into guinea-pigs a filtrate from this culture, marked bronchial spasm was produced. Moreover, this filtrate could be treated chemically to yield, in pure form, the amines which it contained. Experimenting with these purified substances, amines, at different times bronchial spasm and arterial contraction was produced and sometimes both together at the same time. These experiments indicate the existence of active poisons in the bacteria, and the ease with which bacteria can act upon histidine in the culture medium, and, incidentally, in animal tissue, to oxidise it to histamine. They serve to show the widespread occurrence of histamine and emphasize its physiological importance.

Some very interesting work is described by Lewis (101) who has studied the response of human skin and its blood vessels to a variety of different stimuli. He described a reaction which he calls a "triple response". In this, a very light stroke produces

a white line on the skin, due to a contraction of the minute superficial skin vessels; a firmer stroke produces a red line, due to a dilatation of these same superficial vessels, evidently depending upon a direct action on these blood vessels. The second effect, which is slightly delayed in its appearance, is a red "flare", which Lewis showed to be due to a dilatation of those larger arterioles which lie underneath the stimulated area and extend for some distance around it. This dilatation is not due to the direct injury but to a reflex stimulation through the sensory nerve endings, because no "flare" is obtained, even though the red line occurs, if the nerves have been interrupted. The third effect is a local oedema or wheal which Lewis showed to depend upon a direct effect on the capillary blood vessel wall, whereby its permeability is increased. As he discovered that these reactions occurred quite independently of the general circulation to the part concerned, Lewis decided that they could be best explained by assuming the presence of some chemical substance already present in the cell and perhaps released by the stimulus. This he called "H-substance", and concluded that it had a normal

function. The stimulating property of this "H-substance" is evidently concerned with the regulation of local blood flow. It was only to be expected that these observations would be applied to various clinical states. The shock which accompanies wounds is attributed to the wide-spread liberation of "H-substance". In fact, injuries of all sorts may be conceived as leading to the release of this intracellular substance. Although Lewis was very tempted to regard his "H-substance" as identical with histamine, he avoids saying that they are so, chiefly because the reactions to the two substances differ quantitatively.

Now it is known that certain individuals will react to contact with such physical agents as heat or cold to produce a variety of symptoms ranging from asthma to urticaria, Moreover, there is a group of asthmatic patients whose symptoms are brought on by changes in outside temperature, quite apart from bacterial infections.

There has been more interesting work on this same subject. It was found by Harris (102) that an alcoholic extract of the human skin contains a well marked depressor substance, which can instantly produce contractions in the guinea-pig uterus. A year later, in association with Lewis and

Vaughan (103) Harris published an account of cases of haemoglobinuria and urticaria arising from cold. They described some patients who reacted to cold with haemoglobinuria, some with immense local oedema, and some who developed both these signs at once. Moreover, they were able to transfer the sensitiveness to cold from a patient to a normal subject. So they suggested that there must be some substance - a dermolysin - in the blood to account for their findings. Systemic histamine-like reactions in allergy due to cold have been also described in America by Horton and Brown (104).

Toxic substances were found in the blood in cases of asthma, urticaria and migraine by Van Leeuwen and Zeydner (105). Blood was withdrawn from a vein, mixed with alcohol, the alcoholic extract evaporated and the residue dissolved in salt solution. Experiments were done on isolated loops of the intestine of a cat and results obtained comparable to those produced by pilocarpine. The extracts of normal blood, however, had no such effects.

Then in 1930, Barlow and Oriel (106) published their account of the finding of a proteose substance in the urine, reference to which has already been

made. They put forward the view that in chronic or recurrent allergic states, in which the symptoms cannot be ascribed to hypersensitiveness towards one or more known specific antigens, the antigenic moiety of the proteose may be a secondary antigen, produced by the sensitised liver (and possibly by other tissues) on contact with diverse primary antigens.

Therefore it seems justifiable to put forward the theory that anaphylaxis and allergy produce injuries to the tissues; and symptoms arise because the union of antigen and antibody results in a local injury to the cell, whereby a substance is released which the cells normally retain. This non-specific histamine-like substance is activated by specific means. Such a theory would appear to explain how symptom-complexes, like asthma or anaphylaxis, which are so uniform, can be produced by contact with allergens which are so diverse. The whole character of the allergic syndrome seems to point to the presence of a general poison. It is the new knowledge of histamine which provides a new conception of the formation of this poison, and indicates that it may be a substance normally present in the cell and simply released by the injury of the specific allergic reaction.

There is another feature of allergy which is attracting recent attention. Skin tests with histamine tend to show that asthmatic patients give exceptionally strong reactions. Moreover in cases of asthma benefited by treatment, these reactions tend to be much less marked. This is most interesting when it is remembered that animals vary according to species in the degree of anaphylactic symptoms; and more so, because the behaviour towards histamine injections runs parallel to that in anaphylaxis. The guinea-pig is known to be easily sensitised and to be very susceptible to anaphylactic shock. The rat is, on the other hand, completely refractory to anaphylaxis, and has been found to be very much more resistant to histamine than the guinea-pig. Again, it would seem possible to raise the tolerance to histamine, according to the work of Raminez and St. George (107). So that these facts tend to show that the state of allergy is characterised by a diminished resistance to histamine-like substances.

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PROTEIN SKIN REACTIONS.

The employment of the skin test has given to the whole subject of allergy a great impetus in recent years. History-taking, with great care and detail, is a subject of fundamental importance in hypersensitiveness. By its means, it is often possible to discover that a patient's symptoms are being produced by some specific sensitiveness. If the patient be then skin tested with the suspected article, a positive reaction would be valuable confirmatory evidence. The object, then, of the skin test is to demonstrate that the patient reacts to some foreign substance in a way different from normal individuals. Such tests are based on the fact that those substances which, when inhaled, ingested or taken into the body by other means, are capable of producing allergic response, will also produce an urticarial wheal when brought into contact with the lower layers of the epidermis. Skin tests may also however, be used to demonstrate the activity of an allergen by testing it in an individual known to be sensitive to the allergen concerned. The allergens used in skin-testing are generally organic in nature, consisting mostly of protein material. Of

course, non-protein substances, such as aspirin and other drugs, may give rise to allergic attacks when inhaled, or ingested; but they do not produce specific skin reactions.

The mechanism of a skin reaction is twofold. First, there is the local formation of a substance of a histamine-like nature; and then follows therefrom a nervous reflex. It must be borne in mind that the skin of an allergic individual is not any more reactive to ordinary irritants or the process of testing than normal individuals. Another point is that any reaction is entirely specific to the allergen concerned. It has been shown that whereas reactions may occur to whole proteins, they may not occur to the corresponding amino-acids. So the substance that gives rise to the reaction must be contained in either the whole protein or in the products which occur from early katabolism.

The relief of symptoms that follows the removal of the suspected allergen, in a case of a positive reaction, is definite proof of the value of such a reaction. This receives further support if the symptoms are reproduced later, after a free interval, by natural contact with the offending allergen.

It is a well established fact that sensitivity

is most often concerned with environment and diet. Therefore, it is wise to test, in the first place, for environmental factors as suggested by a careful history of the home conditions. Such history should include definite details as to bedding, furniture, room equipment and animals kept as pets or otherwise. When considering the diet factor, a detailed history is again of foremost importance; for obviously if attacks only occur at infrequent intervals, they are not likely to be due to such daily constituents of the diet as milk, eggs, wheat or potatoes. If inhalants, from environmental factors, and foods give negative results, it is well to try for bacterial sensitiveness. More will, however, be said about this latter, presently. In infants, it is well to perform tests for food sensitivity first. The time of year at which the attacks occur may be a guide as to what to test for - winter attacks suggest a bacterial origin, and spring attacks are most often due to pollen.

It is only to be expected that in such a subject the question of the incidence of positive reactions in normal individuals must arise. There is general agreement on this point that such incidence is practically negligible. In any doubtful case, it must

be remembered that allergens are of such widespread and varied character that such an individual may be merely a potential allergic who has not yet encountered the exact substance to which he is sensitive. In other cases, a certain amount of individual tolerance against the specific protein may be present.

The standardisation of extracts and allergens to be used in diagnosis and treatment is an important problem, a satisfactory solution of which cannot be said to have been achieved yet.

The allergens used in skin testing may be in the form of fluid extracts, pastes, dried powders, tablets or filter papers. Some workers employ group reagents, each group consisting of a number of allergens belonging to the same type; for example meat may be beef, mutton, pork or poultry. If a positive reaction is thereby obtained, tests are then performed with individual members of the group.

It is convenient to consider these allergens in four main classes:-

1. Inhalants. Animal emanations.
   Dusts.
   Pollens.
   Fungi.

2. Ingestants. Milk,
Eggs.
Cereals - and nuts,
Meats.
Fish.
Vegetables and fruits.
Drinks.
Yeast.

3. Infectants. Bacteria.
Helminths.
Protozoa.

4. Injectants. Drugs.
Therapeutic sera.
Bites and stings.

This is the classification as suggested by Bray (108).

These tests may be performed either through the skin or through mucous membranes.

Skin method. There are two ways in which the skin may be used for these tests. The first is the cutaneous or scratch method. This consists in applying the allergen to a scratch in the skin. The site of election is the anterior aspect of the fore-arm. Failing this, the outer side of the upper arm, the extensor aspect of the thigh, or the back may be used. The part chosen is best prepared

just before performing the test with ordinary warm water or normal saline. Drops of the solutions of the allergens are then placed one inch apart down the forearm, but not directly below each other, to ensure proper lymph drainage. If powders are used, the technique only varies in the previous application of some solvent such as salt solution made slightly alkaline with sodium hydrate. Using a number 4 straight triangular surgical needle, scratches are then made through the test solutions in a direction parallel to the axis of the limb or part used. No blood should be drawn by these scratches. Endeavour must be made to keep these scratches as uniform in length and depth as possible. The reagents are rubbed into the scratches by a platinum loop sterilized in a flame. A positive reaction begins to appear within two to three minutes as a small urticarial wheal which promptly spreads in all directions, typically with the formation of pseudopodia. The height of the reaction usually occurs in fifteen minutes when the wheal may often measure thirty to forty millimetres in diameter, and may be surrounded by a pink areola which is fifty to sixty millimetres across. No dressing need be applied unless bleeding has occurred.

The second skin method is the Intradermal. This requires more exact technique. The allergen is injected between the layers of the skin with a small gauge needle. The avoidance of trauma is obviously very important. The method of choice is the insertion of the needle through a drop of the allergen. Only one syringe and needle is required if they are carefully washed through solutions of sterile saline after each individual test. The intradermal test is less convenient, and also less convenient to the patient, but the number of positime reactions obtained is greater. General reactions of some severity have been known to occur following its employment. The results of this test are essentially the same as those of the scratch test, except that the wheals appear somewhat quicker and are frequently of large size.

There is one other test, sometimes used, in which the skin is utilized. This is known as the Patch Test. It is used chiefly to determine susceptibility to external irritants, especially those of non-protein nature. The skin of the supra-scapular area of the back is cleansed and a 4 cm. square of adhesive tape is applied. In the centre of this is placed a 1 cm. square of gauze well

covered with the substance to be tested. Between this and the adhesive tape is a strip of lint to prevent any dermatitis. The patch is allowed to remain on for twenty-four hours. A positive test is defined as one in which there is formed a well-marked, infiltrated, inflammatory area covered with papules or vesicles or combinations of these; and it is usually accompanied by pruritus. The patch, if positive, may remain for three to twelve days, some say longer; it may take seventy-two hours to form.

Mucous membrane method. When the skin tests are very weak and difficult to interpret, the conjunctival test is sometimes useful. It is also often used in the determination of pollen sensitiveness. A solution of the suspected allergen is dropped into the conjunctival sac; and the reaction, if positive, appears in five to ten minutes as a diffuse reddening with itching and a watery discharge; sometimes there may be only a tickling of the inner canthus; and on the other hand, the reaction may be so general as to include sneezing. Some investigators consider that the eye test indicates a higher degree of susceptibility. At any rate, owing to the fact that the extract used is

probably stronger than any solution of the pollen, say, that may be encountered ordinarily, a negative test would appear to rule out any active sensitisation.

Sometimes other mucous membranes may be utilised. The nasal test is performed by spraying or insufflating into the nose the test substances, and a positive result is indicated by profuse watery secretion, accompanied by violent sneezing. In the oral reaction, blistering and swelling results from the application of the test substances to the lips and mouth. In the rectum, itching and mucous discharge indicate positive reactions.

The interpretation of these tests. The appearance of the test reaction, when positive, has already been referred to. There are three characteristics:-

1. a central branched wheal;
2. irregular pseudopodia, extending from the wheal, and a
3. surrounding Erythema.

A positive reaction shows any of these or all three, The area of the test is frequently hot to the touch and often characterised by burning and itching.

There is no doubt that these skin reactions vary widely. The irritability of the skin may

range from a slight redness around the site tested to an intense exaggeration amounting almost to true dermographism. Furthermore, this irritability may change from time to time in the same individual. Why this should be so is unknown. It does not follow that all positive results are true specific reactions. Therefore it is always advisable to substantiate any opinion that contact with the allergen causes an allergic syndrome and to observe the effect produced by removal of the offending allergen, if possible. Histamine is known to give positive reactions in all persons, and pseudo-reactions may be due to its liberation. All doubtful reactions should always be recorded and retests made at some future date, when comparison will be found most useful. It is obviously important that the technique should be as uniform as is possible. Positive controls have been used by some workers and found very helpful The most efficient appears to be codeine sulphate. If this is applied to a scratch in the skin, what amounts to a "positive skin test," results. Such a control is useful to show that negative results are truly negative, and for the purposes of demonstration.

Sometimes severe allergic reactions follow these tests, such as asthma and urticaria. Such are useful confirmatory evidence. They can, however, be alarming; and it is wise to have always at hand a 1-1,000 solution of adrenalin hydrochloride, the injection of ½ c.c. of which will usually abort any symptoms.

Delayed reactions to tests with common allergens have been known to occur. So the patient should be instructed to watch for and report any changes which may occur within twenty-four hours or thirty-six hours.

There are certain factors which definitely influence positive results. The most important of these is (a) Age. Patients over forty-five years of age rarely give a positive reaction; whereas about eighty per cent. of cases of asthma beginning in infancy are sensitive. These cases of asthma in infancy show another interesting factor - they are very often cases of food sensitisation. As age advances, so the tendency to food sensitisation diminishes. The next point to influence results is the (b) Type of skin. Reactions on dry skins are very weak and sometimes non-reactive. If a skin is eczematous, the reaction may spread over large areas.

(c) The site of application may also affect the result. For the skin at the bend of the elbow is very much the most sensitive. (d) Reference has already been made to the influence of the method employed. It was pointed out that the intradermal test gives a greater percentage of positive results than the scratch method. Another important influencing factor is (f) the type of case. In cases of asthma that follow acute respiratory diseases, with a negative family history, positive results are difficult to obtain; whereas in cases with well-marked family histories of allergy, and in which eczema occurred in infancy, a positive result is relatively easy to obtain. (g) The greater the number of allergic manifestations displayed, the more likelihood there is of a positive skin-test being obtained. (h) Drugs appear to lessen definitely the reactivity of the skin to testing and should therefore not be given for at least twenty-four hours beforehand. It is said that alkalies increase sensitivity, but that ephedrine and adrenaline decrease it. (i) The tests are best performed just before or at the beginning of an allergic attack, because following an attack all reactions may be negative owing to temporary desensitisation.

Much discussion has taken place as to the relative merits of the various test methods. The methods all have their uses. When a patient is obviously sensitive, the scratch method is adequate for confirmation. Should it fail, then the intradermal may be employed. When, however, nothing in the history points to an extrinsic factor, and the object of the tests is to rule out the possibility and prove that the patient is not sensitive, then the intradermal method is the one of choice.

The question of the use of bacteria and their extracts for skin tests merits some attention. Mackenzie and Hanger (109) showed that bacterial skin tests were negative in children and positive in adults, and therefore showed that the individual had previously suffered from an infection with that organism or another related to it. Instead of the immediate urticarial response observed in the ordinary allergens, such as pollen, the local reaction with bacteria is delayed for twenty-four hours or more and then appears as a local inflammation. In some patients, however, an immediate wheal has been obtained; this would appear to be usually the case if the bacterial test is made with the autogenous vaccine derived from an existing infection. In some cases, again, the two types of reaction may

appear. Recent work by Zinsser (110) and his co-workers, and by Enders (111) has stimulated afresh the interest in the whole subject of bacterial allergy. These observers have now shown that such a substance as tuberculin consists of two parts:-

1. one which causes anaphylaxis and cell-sensitisation, called "proteose residue";
2. another which also sensitises cells but produces a slower reaction, which is a nucleo-protein.

Avery (112) and his associates have further shown that if a chemically pure sugar radical is added artificially to a simple serum globulin, a new complex protein is formed which has its own biological specificity. In other words, specificity depends on chemical structure and especially on the carbohydrate radical. And this carbohydrate substance merely determines the specificity of the immediate anaphylactic or allergic reaction. It differs in the various strains of bacteria and determines their biological specifity, and has no antigenic properties. The delayed inflammatory reaction is obtained with the whole bacteria or their nucleo-protein part. Such findings as these appear to account for the indefinite results obtained with bacterial tests in patients classified as "bacterial" clinically.

This discussion on protein tests would not be complete without a reference to what is known as the Prausnitz-Kustner Reaction. This was discovered in 1921 when the serum of Kustner, who was sensitive to fish, was introduced into the skin of Prausnitz; and a local and passive sensitisation to fish at the injected site was discovered by intradermal test. The technique is as follows:-

"5 to 10 c.c. of blood is withdrawn from the patient, defibrinated, centrifuged and the serum pipetted off and passed through a Berkefeld filter. This serum is then ready for use and may be stored in an ice-box, its activity lasting for about six months. To perform the test, inject into the skin of a chosen person one twentieth to a tenth of a cubic centimetre of this serum in one or more injections, the serum being diluted ten times. Outline the area injected in ink, as the serum is absorbed rapidly. An interval of about two to three hours or more should be allowed, for the serum to be absorbed completely. Then test each site with the suspected specific protein. In the case of suspected food proteins, these should be excluded from the diet for twenty-four hours; and the following

morning, the protein should be taken on an empty stomach. A reaction, if positive, develops at the sensitised site in from a few minutes to two and a half hours after the completion of the injection or meal. Within one to eight hours after the onset the reaction has completely vanished."

It has been shown that sensitisation may remain in injected sites for about four weeks; so that it is not necessary to perform the reaction at once. Once a positive reaction is obtained, the sensitivity of the site is generally lost; sometimes its reactivity may gradually diminish on succesive applications.

The value of this reaction lies in its application in cases where the usual skin tests are not practicable. Such cases are infants, patients unable to attend through illness or distance, very nervous patients, others with gross skin lesions, and those with extremely dermographic skins. For it is possible to sensitise locally and passively to a certain protein the skin of almost every person by the intradermal injection of such a serum taken from hypersensitive patients, so that the subsequent injection or ingestion of that protein will produce a wheal at the sensitive site.

Now the accuracy of skin tests undoubtedly varies with the substances used. With pollen and animal epithelia, it may be said that they are extremely accurate; if positive, they almost invariably indicate a causative factor in the patient's trouble. On the other hand, food tests are much less reliable and are apt to give different reactions at different times; milk and eggs in children are much more reliable for test purposes than any food stuffs in adults.

In summary, it may be said that a positive skin reaction indicates:-

1. A definite sensitivity to the protein concerned, although this protein may not actually be the cause of the present condition;
2. A latent sensitivity, latent because the individual concerned has not, up to the time of testing, been in contact with the offending allergens;
3. A specific sensitivity, in that the individual can be relieved of his condition by eliminating or desensitising him with, the protein to which the positive skin test was obtained;

On the other hand, a negative skin test may be taken as indicating:-

1. A true absence of sensitivity;
2. A pre-sensitisation stage, in which sufficient

sensitivity has not so far been acquired as to react with the allergen applied locally.

In such a summary, it must always be borne in mind that these tests depend to a great extent on the reliability of any extracts used.

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BIOCHEMISTRY OF ASTHMA.

There has always been a great diversity of opinion about this subject. Various observers have published findings, which have not met with universal approval. No doubt such a state of affairs must be due to a lack of uniformity in technique, a lack of completeness of investigation and to errors in diagnosis. Nevertheless, there are now certain well-established facts which will be discussed.

The first what may be called biochemical observation was made by Ringer in 1864. He recorded the fact that immediately following an attack of asthma there was a marked dimunition of urea and chlorides in the urine, obviously suggesting some profound metabolic disturbance. Since then suggestions have been put forward at odd times up till 1920, when there began a period of intensive laboratory investigations. As a result of the latter, the whole subject has been placed on a much sounder basis. It has been found that there definitely exists what might be called a "biochemical formula" for all allergic diseases, a very significant fact when it is recalled how very

varying the clinical manifestations may be. Another very important finding is that so far as biochemistry is concerned it is possible to recognise three stages in an allergic attack - the pre-paroxysmal, paroxysmal and post-paroxysmal. And merely from a biochemical examination of the blood and urine, it is possible to tell in what stage the patient was when the specimen was taken.

Biochemistry of the Blood.

Amino-acid Content.

The average normal figures for the amino-acid content of the blood are from 4.0 to 6.5 mg. per 100 c.cm. A slight temporary rise occurs after a protein meal in normal subjects and in others. So Barber and Oriel (72) suggest considering figures above 7 mg. per 100 c.cm. as a raised content. Working on this as a standard, they found that during the acute paroxysms of asthma the amino-acid content of the blood is raised. In the intervals between attacks, they find a raised amino-acid content in the type of asthma, beginning in infancy and associated with eczema, whereas in the type beginning at puberty or the climacteric and generally following an acute infection involving the respiratory tract, they find the amino-acid content is normal. At

any rate, the amino-acid content of the blood appears to be increased more often in persons with multiple allergy and in those in whom there is a family history of allergy, than in persons in whom there is none.

These findings have been confirmed by Cameron (73). So that the amino-acid content of the blood varies with the allergic state. Cessation of asthmatic attacks following treatment is accompanied by a normal amino-acid content.

A raised amino-acid content of the blood is known to occur in anaphylactic shock, and in experimental intestinal obstruction, the latter of which is said to be due to a proteose intoxication.

Blood Chlorides.

It is necessary to distinguish between the whole blood chloride content and the serum content, because normally the serum chloride exceeds that in the corpuscles. The normal limits are:-

per 100 c.cm of serum - 570 to 585 mg. per 100 c.cm.
and per 100 c.cm of whole blood - 455 to 495 mg. per 100 c.cm.

In acute and chronic allergic conditions, Barber and Oriel (74) find that the whole blood chlorides are markedly diminished during the paroxysms, and that the reduction of the corpuscle content is greater than that of the serum content.

This reduction seems to vary with the activity of the allergic state.

Bray (75) states that his results confirm Barber and Oriel's figures.

It has been suggested that the chlorides possessed the property of shifting from the blood to the other tissues in order to preserve the optimal osmotic conditions of the blood.

A dimunition of blood chloride also occurs in experimental high intestinal obstruction. Symptoms produced by such obstruction have been attributed to proteoses, absorbed through the damaged intestinal mucosa. Haden and Orr (76) suggested that the chloride was utilized to neutralize these proteoses. It is of interest to record that Richet showed that experimental anaphylactic shock could be prevented by the previous injection of sodium chloride.

Blood Sugar.

The normal blood sugar is 90 to 110 mg. per 100 c.cm.

All investigators appear to agree that in allergic conditions the blood sugar tends to be below the normal, in many cases as low as 20 mg. per 100 c.cm. below.

As a group, there is a tendency for the early production of ketosis from slight causes.

Blood Cholesterol.

This has attracted the attention of various continental observers. And certain American workers describe an increase in blood cholesterol during every asthmatic attack. Cameron was of opinion that the cholesterol content varied with the resisting power of the individual. Whereas he found values above normal, Bray was unable to confirm this.

The normal blood cholesterol is 150 to 200 mg. per 100 c.cm. It tends to rise as recovery from acute infectious diseases occurs, and is apparently related to the defence mechanisms of the body. It is most interesting to record that the suprarenal cortex enlarges during pregnancy when there is also a well-marked hypercholesterolemia.

Acid-Base Equilibrium.

If in a solution the pH exceeds 7, such is alkaline; if it is less than 7, it is acid.

The reaction of the blood is the degree of acidity or alkalinity as determined by the H ion concentration. Acidaemia is a condition in which the H ion concentration is increased; alkalaemia is one in which the H ion concentration is below normal.

Alkalaemia occurs at high altitudes.

Acidaemia may be due to (a) a diminution of the bicarbonate content of the blood, or (b) to an increase in the carbonic acid of the blood. In emphysema, the CO_2 tension in the alveolar air is increased and there is an increased bicarbonate content of the blood.

The urinary "ammonia" is increased in acidaemia.

It would appear that there is a definite acidaemia during an asthmatic attack. Spangler (77) described a slightly larger range in the H ion concentration in allergic individuals. Bray found that the plasma bicarbonate content is toward the higher limit of normal, and is generally higher in allergic than in non-allergic children.

Blood Calcium.

The normal serum calcium is about 10 mg. per 100 c.cms. The calcium content of the corpuscles has not yet been carefully studied. A lowering of the serum calcium leads to hyperexcitability of the motor nerves and of the central nervous system - that is, to tetany. It may be due, amongst other causes, to increased alkalinity of the blood.

The level of the blood calcium is normally

very constant and not easily disturbed, except by such extreme conditions as persistent vomiting, which results in a loss of total base. Calcium came to be used in allergic conditions on purely empirical grounds. According to recent biochemical investigations, variations from normal values of blood calcium are not outstanding.

As long ago as 1881, Ringer observed an antagonism between the calcium and potassium ions in the cells. The former decrease nerve irritability and so act in harmony with the whole sympathetic system. The sodium and potassium ions, however, increase nerve irritability and their effect may be compared to that of the whole vagus system. Pottenger (78) suggested that the calcium treatment of allergic conditions was not unreasonable on the following grounds:-

1. asthmatics have a vagotonic character;
2. the vagus nerve is over active in many ways to produce a variety of symptoms;
3. the increased effects are comparable to a theoretical increase in potassim ions;
4. such an increase as latter must be accompanied by a decrease in the calcium ions;

He reported successful treatment with calcium intravenously. Attempts to confirm this work

have, however, failed. Various observers have arrived at the same conclusion, namely, that patients suffering from the various clinical manifestations of allergy have a blood calcium which closely approximates the normal. Criep and McElroy(79) concluded that a deficiency of the blood calcium cannot be found to exist in allergic conditions and that calcium therapy does not seem to produce a permanent increase in the blood calcium of allergically sensitive patients.

There is another point in this subject of blood calcium. Serum calcium can be divided into (a) diffusible and (b) indiffusible components. The former may be further subdivided into ionized and un-ionized fractions. It should be remembered that a reduction of the ionized calcium may occur without there being necessarily any alteration in the total serum calcium; and it is probably this ionized calcium which is of special functional importance. Recent work by Cantarow (80) would seem to suggest that the calcium in the cerebro spinal fluid is similar in quantity to the diffusible calcium in the blood; that the spinal fluid calcium is higher than normal in most cases of asthma; and that the ratio between the spinal fluid calcium and the blood serum calcium was higher than normal.

And he considers that this latter ratio is an expression of the distribution of calcium between tissues and capillaries. Such a suggestion is in line with Manwaring's (81) original idea that increased capillary permeability is a factor of fundamental importance in protein sensitisation.

There is another recent finding of importance; and this is by Peters (82) and his associates, who have shown that the level of blood calcium is closely dependent upon the level of serum protein and of phosphorus. It is known that the calcium in the blood serum varies inversely with the phosphate, and falls when phosphate is injected. On the other hand, proteins increase the solubility of calcium; so that the calcium varies directly with the concentration of total protein in the serum. Therefore it is necessary to observe at the same time as the calcium level is being investigated, the phosphorus content and the total protein content.

In spite of all these investigations, odd cases of asthma are definitely improved by intravenous injections of calcium chloride. Any benefit thus obtained would seem now to depend upon the general shock of the injection, with its

marked general disturbance, rather than be due to any specific effect of the calcium.

Biochemistry of the Urine.

This subject has received a great deal of attention of recent years, particularly as a result of the investigations of Barber and Oriel (83). It is maintained, that, in a patient with allergic symptoms, an examination of the urine will reveal whether that patient was just starting a paroxysm, was in such a paroxysm or was in the period following it. And vice versa, it is possible to predict the urinary findings from the condition of the patient at a given time.

Patients with allergic symptoms display two very important and almost constant phenomena at certain times, during the period of active manifestations. These are:-

1. the ether reaction, and
2. the deposition of urates or uric acid in the urine on cooling.

The former was first observed by Oriel in cases of cardiac failure with oedema. It is, however, a reaction which occurs with great frequency during allergic conditions. The urine is acidified with sulphuric acid and shaken with a fifth of its volume of ether; an ethereal layer forms on standing, which, instead of being for the

most part clear as in normal people, becomes opaque and has a waxy appearance. In fact, in strongly positive cases, the tube in which the test is made could be inverted without spilling the contents. If this reaction is carried out in a separating funnel and the lower layer run off, the supernatant layer, when shaken with an equal volume of alcohol, yields a precipitate of a complex nitrogenous substance, the interesting biological properties of which will be discussed later. Oriel states that the reaction is always strongly positive during the acute phase of allergic manifestations but may disappear during the period of quiescence. It is very marked after a anaphylactic shock. It would appear that there is some connection between this reaction and the deposition of urates, both being probably dependent on an alteration in the colloid state of the urine.

The deposition of urates. The usual teaching is that this is due to (a) the concentration, and (b) the acidity of the urine. Oriel considers that both these factors are of relatively minor importance. The dominant factor is apparently the state of the urine colloids. The precipitation of urates does not depend upon the uric acid itself;

stones composed of uric acid are most frequently found in children, although true gout is extremely rare in childhood. Urates are more commonly deposited in the night or early morning urine. Deposition of urates is known to occur in the urine of apparently normal healthy people, but this is rare and would seem to suggest a temporary functional metabolic disturbance. Patients with cirrhosis of the liver, those with hepatic degeneration accompanying heart failure, and those with such acute infections as pneumonia frequently show uratic deposits. In fact, Price (84) regards an excess of urates as evidence of heart failure. In allergic diseases, this deposition of urates is so frequent as to be almost constant in some period in the twenty-four hours, at least during the phase of active manifestations. There must be some alteration in the colloidal state of the urine which predisposes to the deposition of urates, in these allergic diseases.

Urinary acidity. This varies according to the particular phase in which the allergic patient happens to be at the time it was collected. Just before a paroxysm it is raised slightly; but as the attack proceeds and passes off, it falls; the

urine then tends to become neutral and sometimes strongly alkaline with a deposit of phosphates. The urine is usually concentrated when it is acid; once alkaline, it is dilute. After asthmatic attacks, a diuresis is known to occur.

Ammonia excretion. This does not correspond with the degree of acidity, a rather striking feature of the allergic state. The normal ratio between the free acid and the ammonia-combined acid, according to Davis and Rixon (85), varies from 1 : 0.6 to 1:1.5. In patients with allergic symptoms, the ammonia excretion is raised, often to extraordinary extent, and the above ratio is found to be abnormal at the period of and following the paroxysm. It may be as high as 1:7 for example.

Not only is the ammonia excretion raised in association with the paroxysm, but also the creatinine and uric acid.

During the active stage of an allergic attack, there is a low excretion of chlorides in the urine; after the paroxysm is over, the excretion rises. It is interesting to note that a complete absence of chlorides in the urine has been observed in anaphylactic shock and serum sickness.

Now may be summarised the cycle of events that occurs in all acute allergic conditions, in the blood and urine.

1. In the period just preceding and during the paroxysm.

Blood.	Urine.
1. The amino acid content rises.	1. The free acidity rises.
2. The uric acid and creatinine are apparently increased.	2. Urates are often deposited when the urine cools.
3. The chloride content of the whole blood falls.	3. Diminished water excretion, so that the specific gravity is usually high.
	4. Retention of chlorides.
	5. Ether reaction strongly positive.
	6. Ammonia excretion rises and the ratio of free acid to ammonia-combined acid is altered.
	7. Excretion of amino-acid creatinine and uric acid begins to rise.

2. In the period following the subsidence of the paroxysm:-

Blood.	Urine.
1. The amino-acid content falls.	1. The free acidity falls, and the urine tends to become neutral and finally alkaline.
2. The uric acid and	2. The excretion of

Blood.	Urine.
	volume is raised and the specific gravity falls.
3. The chloride content of the whole blood rises.	3. Excretion of chlorides is increased.
	4. Ether reaction diminishes and may entirely disappear.
	5. The excretion of ammonia begins to fall, but not correspondingly with the excretion of acid, so that the ratio of free acid to ammonia-combined acid is still further altered.
	6. The excretion of amino-acid, creatinine and uric acid gradually falls.

In discussing the ether reaction, reference was made to the presence of a complex nitrogenous substance in the urine of allergic patients. This substance appears to belong to the ill-defined group of the proteoses. It has been the subject of much investigation by Oriel (86). An aqueous solution of this substance gives a positive Biuret and Millon's test and a positive reaction for the presence of carbohydrate. By estimating the total nitrogen excreted daily and comparing it with the total proteose nitrogen a ratio may be established. In normal individuals, the highest ratio of this nature was 0.28 per cent, whereas in asthmatic patients this was 4.4 per cent. Between attacks the output of proteose nitrogen

in asthmatics falls to normal levels. A simple method of preparing this proteose for skin-testing and desensitisation has been devised, which it is as well to give in detail:-

"The urine passed just before and after an attack of the allergic paroxysm is collected, and a few drops of chloroform added to prevent putrefaction. Four hundred cubic centimetres of this urine are taken and the reaction adjusted to P_H 5 with dilute sulphuric acid. If urates are present as they often are before an attack, the urine is first neutralised with caustic soda, as it is then found that the urates do not precipitate again on acidfying with sulphuric acid. The acidified urine is shaken with 80 to 100 c.c. of ether. After separating, the lower layer is run off and the upper layer is shaken with an equal volume of absolute alcohol. The precipitate obtained is collected in a centrifuge tube, suspended in sterile water and again centrifuged. It is then suspended in sufficient N/10 NaOH to render it alkaline, and made up to 10 c.c. in a sterile Wright's vaccine bottle with 0.5 per cent phenol in buffered saline. It has been found by estimating the nitrogen in this solution that there is very approximately an average of one part of proteose

in 1,000 c.c. of solution, and this stock solution is therefore known as the $\frac{1}{1,000}$ dilution."

Oriel (87) suggests that the proteose contains the specific antigen to which the patient is sensitive. His reasons for this suggestion are as follows:-

1. Each asthmatic patient gives a positive skin reaction to his own protein;
2. the protein obtained from a patient suffering from serum sickness gives a positive reaction when injected in very small quantities into a known "horse-asthmatic";
3. the Prausnitz-Kustner reaction can be obtained with this proteose; serum from an allergic patient is injected into the skin of a normal man; on subsequently injecting into this area a dilute solution of proteose from the urine of this same allergic patient, a positive reaction is obtained in the injected area but not in the untreated skin;
4. when proteose is injected into the patient from whom it is derived in doses of one ten-millionth of a gram, acute attacks of asthma may be induced, whereas large doses have no effect on an unsensitised animal.
5. proteose from one asthmatic or allergic

individual does not necessarily give a positive skin reaction in another allergic patient; in fact, asthmatics are usually insensitive to proteose from other asthmatics.

No doubt this work is open to much criticism. At the same time, it would appear to be of great value. It is known that a small quantity of proteose can be recovered from the urine of a normal person in apparent health. Such a proteose in such an individual however, does not give rise to a positive skin test. It is the antigenic part of the proteose excreted that is of importance. Again, it is the proteose obtained during the stage of active symptoms that matters, for that collected during a quiescent period may give negative results. It must not be overlooked that a relatively large quantity of proteose may be excreted in the urine in acute infections, in anaphylaxis and in acute and chronic allergic conditions.

The significance of this proteose in relation to experimental findings in animal anaphylaxis will be discussed later. Its importance lies in the fact that it is a definite substance; it would appear to contain the specific antigen upon

which the symptoms depend in some acute and chronic diseases and so can be used for desensitisation purposes. In fact, it may even be "the long looked-for link between the glass of milk and the colloido-clasic crisis."

The blood in Allergic Conditions.

The study of the blood in allergic conditions has been vigorously carried out by many French observers, chief among whom is Widal (88). They describe various changes, but emphasize the importance of two. These are:-

1. a drop in the arterial pressure;
2. a dimunition in the white cells.

Among the others described are - an inversion of the leucocytic formula, a change in the colour of the blood, modifications in blood coagulation, a considerable drop in the refractive index of the serum, and the presence in it of dialysable albumens. They group all these modifications of the blood under one heading, which they term "colloido-clasic shock". These findings have not, however, been completely corroborated. The blood clots in normal time; and the balance of opinion does not favour any alteration in the coagulation time.

Oriel (89) states that the blood taken before

an attack of asthma has a reduced sedimentation rate, whereas after an attack the rate is increased. This sedimentation rate of the red cells may be inversely proportioned to their number and directly proportioned to the relative number of leucocytes. There is undoubtedly an increase in the concentration of the blood during allergic conditions, which probably results from the transudation of serum into the local lesions. It is well to remember that one of the mechanisms to compensate for the difficulties with respiration in asthma and emphysema is a polycythaemia, by which a given volume of blood can increase its number of red corpuscles and consequently its content in haemoglobin so as to carry more oxygen.

The fragility of the red blood corpuscles is within normal limits, complete haemolysis mostly taking place in 0.33 per cent. sodium chloride.

There is also nothing abnormal to note about the blood groupings of allergic patients.

Serum and Plasma changes. In the majority of of cases, the refractive index is greatly lowered during the allergic paroxysm. There is also a drop in the pH of the blood in the attack. The alkali reserve may fall from 60-65 to 56-45 volumes of carbon dioxide per cent.

Blood pressure. There would appear to be very varied opinions on this subject. It is, however, common to find a low blood pressure in asthma, at any rate during the attacks. The mechanism by which this is brought about would seem explanatory in itself. The rise in intrabronchial pressure in asthma must interfere with the flow of blood through the lung capillaries and cause a damming back of blood on the venous side; and so the flow to the left auricle must be impaired, and consequently the output from the left ventricle must be diminished.

Blood formula. It is claimed by the French investigators that the white blood corpuscles fall 2,000 or more per cubic millimetre of blood at the onset of the allergic paroxysm occurring before the clinical phenomena. Except in one case, Bray (90) was unable to confirm this. In the differential count the French maintain that the neutrophils are mostly concerned in the leucopenia, with a relative increase in the mononuclear cells. At the onset of an allergic paroxysm, however, it appears that the polymorphs are increased totally and relatively, and the lymphocytes reduced in numbers, the large mononuclears remaining about the same. Most observers record a change to the left in the

Arneth count, most intense at the height of the leucopenia. Following the allergic reaction there is frequently a rise in the number of leucocytes far greater than the number present before the crisis. This is termed a reactional leucocytosis.

Owing to the relative loss of plasma through the dilated capillaries, a slight rise occurs in the haemoglobin percentage during the crisis of an allergic attack. Moreover, the concentration of the blood tends to accentuate this.

The change in the colour of the blood described is common in the condition of shock, in which the venous blood becomes more red. This may be accounted for by the dimunition in the alkali reserve and carbonic acid content.

There is also said to be a dimunition in the number of platelets in the circulating blood.

Eosinophilia. An increase in the blood eosinophiles is characteristic of hypersensitiveness. It is well known that such an increase occurs in animals and man following the injection of foreign protein substances. Although this increase also occurs in asthma between attacks, it is difficult to exclude all influence of the attack itself in its production. It was suggested by Spangler (91)

that the eosinophilic index might be taken as an indication of the reactive power of an individual. This idea is not accepted by many other observers, however. The French maintain that the eosinophil cells are most often concerned in constructive processes in the body, thus differing from the neutrophils which are chiefly concerned in the processes of elimination. In allergic conditions, eosinophils occur at the site of reaction, in the sputum and in the skin lesions. According to the French view, the local eosinophilia is the main factor and the blood eosinophilia a subsidiary one. And they suggest that the eosinophil cell may be something to do with the vagotonic state and not a part of the allergic syndrome at all.

The fact remains that in asthmatic patients the percentage of eosinophil leucocytes in the blood is usually about five - at any rate, in the intervals between attacks, and in the normal individual the percentage is usually one to three.

It may be that there is a local concentration of eosinophils at the site of reaction during the attack, and that once the attack has subsided these are liberated into the general circulation. The fact that during an allergic paroxysm the eosinophils

in the blood decrease and increase when the attack is passing off would seem to substantiate such a view.

The stomach in Allergic Conditions.

Many observers have reported a deficiency in the hydrochloric acid of the stomach in cases of asthma and other allergic conditions. Among these is Hurst (92), who found, in a study of sixty-one adult cases of asthma, that the deficiency of acid was encountered in about twenty per cent. more asthmatics than normal individuals. In a study of two hundred cases, Bray (93) found that in four out of every five asthmatic children the response of acid gastric secretion was below the average normal. He also states that in about fifty per cent. of such children's parents, who show some allergic responses themselves, some deficiency of secretion is noticed. Oriel (94) and his co-workers have been unable to confirm these findings in adults. Cases of hypochlorhydria occurring in asthma are referred to by them; but they consider the low acidity in such patients to be due to a secondary gastritis and not constitutional. It is interesting to note that the hypochlorhydria in childhood is most frequent in the earlier years of life, when food sensitisation is most frequent.

The Liver in Allergic Conditions.

In a previous section the liver was referred to as the site of the anaphylactic reaction in dogs. This was shown by Manwaring (95) and his associates. Hence it is not to be wondered at that this organ should be held responsible for the production of allergic symptoms in man. It is an organ of complex structure, with very varying functions. One of its great characteristics is its ability to tolerate extensive injury and still retain its power to regenerate. Because of its character and manifold functions, it is a most difficult organ to investigate biochemically, and liver functional tests have become notoriously unreliable. There is, however, one test which is apparently coming to be generally used and acknowledged as trustworthy - this is the Laevulose Tolerance Test. It is performed in the same way as the glucose tolerance test is in cases of glycosuria. The patient is bled, 100g. of laevulose dissolved in water are given by the mouth, and specimens of blood are with-drawn at half-hourly intervals for two hours. The results are plotted on a curve. If the blood sugar rises above 140 mg. per 100 c.c., or if the rise above the first value be over 30 mg., then hepatic inefficiency is

present. This test shows the power of the liver to absorb and store large quantities of laevulose, the liver being the dominant organ in sugar metabolism. Bray did a series of fifty-five cases and in twenty-three the curves were abnormal.

A laboratory test to determine the amount of bilirubin in the blood - such as the Van den Bergh-reaction is also most useful. This reaction distinguishes two types of bilirubin:-

(a) one resulting from the breakdown of haemoglobin during rapid haemolysis in the blood stream or in serous cavities;

(b) another which has passed through the liver cells into the bile or else has been shunted back into the blood stream because of obstruction to the bile passages.

The former gives an indirect reaction, and the addition of alcohol to the testing solution is necessary to bring it out. With the latter type of bilirubin, a direct reaction is obtained which may be immediate, delayed or biphasic. Bray was unable to obtain an immediate positive direct reaction. Oriel, on the other hand, claims that twenty per cent. of cases of a certain type of asthma, namely the type in which asthma follows skin complications at an early age, give a positive Van den Bergh reaction. In the usual type of

asthma, occurring at puberty, the climacteric or following some acute infection of the respiratory tract, the reaction is generally negative.

Summary of Biochemistry.

The biochemistry of allergic individuals therefore shows certain definite characteristics. These are:-

1. low Blood sugar;
2. a low cell chloride content;
3. a high amino-acid content of the blood;
4. a normal blood cholesterol;
5. a normal blood calcium;
6. blood phosphorus figures inclined to be lower than normal;
7. during the attack a complex nitrogenous substance of a proteose nature, the specific allergen, is secreted in the urine;
8. Also during the attack the urine shows:-
   (a) increased free acidity;
   (b) increased specific gravity;
   (c) deposition of urates;
   (d) retention of chlorides;
   (e) increased ammonia excretion.
9. gastric analyses show deficiency of acid secretion.
10. liver function tests indicate some hepatic insufficiency.

In the allergic state, whether it is intermittent, or whether it be more or less chronic

with periodical excerbations and remissions, there can be recognised a definite cycle of events corresponding to the pre-paroxysmal stage, the actual paroxysm, and the post-paroxysmal stage. It is interesting to reiterate the striking similarity of the findings in anaphylactic shock.

Some observers, notably Oriel, consider that asthmatics do not fall into one biochemical type. Their two divisions are:-

(a) those which commence as infantile eczema, or are complicated by other allergic manifestations, about twenty per cent;

(b) uncomplicated asthma, following directly on an attack of whooping-cough, bronchitis, pneumonia, or some such acute infectious disease involving the lungs about sixty per cent.

The biochemical distinguishing features are that in the former there is a positive Van den Bergh reaction and a high amino-acid in the blood during the active stage, in the latter a negative reaction and normal amino-acid content. The urine also shows changes of different kinds in both types; in type (a) the urine is very concentrated and amount passed about half the normal of 50 ozs. in the 24 hours; in type (b) there is a relatively

high ammonia-combined acid content, low urea concentration, and the volume passed about normal.

The raised amino-acid content of the blood results from:-

(a) the increased endogenous katabolism, as shown by the increased formation of creatinine;

(b) the relative temporary hepatic insufficiency caused by the damage to the liver cells;

(c) the interaction of the antigen and ferments whereby amino-acids are formed - a doubtful theory.

In any case there is evidence of a disturbance of liver function, as follows:-

1. a positive Van den Bergh reaction - in certain cases;
2. a raised amino-acid content of the blood;
3. probably the increased ammonia excretion in the urine:
4. the precipitation of urates in the urine;
5. the ether reaction in the urine;

The increased ammonia excretion and the temporary retention of chlorides are probably protective mechanisms.

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FOOD ALLERGY.

Foods form a group of substances which can produce definite asthmatic symptoms. This is particularly the case in children, in whom the offending substances are usually eggs, cow's milk and wheat. Indeed, the instances in which foods other than these three have caused definite asthma are few. In adults foods may cause trouble, but only in a comparatively small number of patients. Although positive reactions to foods are not uncommonly found in routine skin tests, it is only rarely that a definite relationship can be demonstrated between the food and the production of symptoms. True it is that many observers have reported improvement in their patients when particular foods have been eliminated from their diets. More important, however, are the other reports of improvement when certain common foods, like eggs , wheat and milk, are eliminated, regardless of whether these foods reacted to skin tests or not. Rowe (113) definitely claims that great benefit can be derived by the use of elimination diets in certain patients with allergic diseases, particularly migraine and urticaria. O'Keefe and

Rackermann (119) report satisfactory results in children with eczema.

Recently interest in this subject has been intensified, and Rowe has translated into English the leading monograph on the subject by the French authors, Laroche, Richet and Saint Girons; this is "L'Anaphylaxie Alimentaire", to which reference will again be made.

Allergy which is manifested solely or even chiefly by gastro-intestinal symptoms is very unusual. Yet in a few patients, the criteria of allergy are fulfilled in that their symptoms, such as obscure abdominal pain or diarrhoea, follow the ingestion of certain foods; that these symptoms disappear when these foods are avoided; and that positive skin tests to extracts of these foods are obtained in these patients. A very important article was published by Osler (115) in 1914, concerning the visceral lesions of purpura and allied conditions. He pointed out the similarity between these patients with hay-fever and sensitiveness to iodine and shell fish. He suggested that the cases he described might well illustrate anaphylactic phenomena in sensitive persons. In 1919, Laroche and his associates

(116) published "L'Anaphylaxie Alimentaire". They demonstrated that guinea-pigs and other animals could be actively sensitised to eggs or milk by feeding them with these foods. They maintained that in an animal or man already sensitised, the ingestion of food could produce symptoms.. Now it is known that asthma, urticaria and eczema may follow the ingestion of certain foods. The French, however, describe further a condition called "La Grande Anaphylaxie Alimentaire", which is really a general reaction to shock. The attack may begin in an adult or child with vomiting and severe abdominal pain of cramp-like, colicky nature. Diarrhoea, collapse with rapid weak pulse, fall in temperature and clammy perspiration may occur, and asthma may be produced. The important diagnostic feature which occurs in most of the cases is an associated urticaria which may begin at once after the meal and may cover the whole body. In the absence of any rash, the diagnosis would be obviously difficult. In this food allergy the attack usually passes off in six to seven hours, particularly if adrenaline is administered. The French designate "Petite Anaphylaxie" cases in which there is no real shock but abdominal pain,

slight or no diarrhoea and little or no urticaria. There is also a chronic and recurrent form of food allergy in which the symptoms depend upon the repeated ingestion of small quantities of the food to which the individual is hypersensitive. These latter cases are characterised by attacks of pain and diarrhoea which usually occur together without any obvious cause.

The mechanism of these abdominal symptoms is not clear. Mainwaring(117) has shown that in dogs anaphylaxis is associated with great congestion of the splanchnic area and frequently with minute haemorrhages in the intestinal wall. The increased permeability of the intestinal capillaries may be a factor. The finding at operation of local areas of oedema in the bowel wall, as described by Osler, confirms the supposition that wheals occur internally, corresponding to the skin manifestations.

In these cases, X-ray appearances almost invariably suggest a spasm in some part of the bowel. Laroche and his co-workers concluded that food allergy may result from too rapid absorption, ineffective digestive juices, the production of special fermentations, the presence of toxigenic substances in the blood, or a condition of non-immunity.

These abdominal symptoms so far described are very common in childhood. A bloody diarrhoea has been mentioned in some reports. And the ingestion of milk in hypersensitive infants and children is even said to have caused death. It may be that many children who show disinclination for certain foods are merely protecting themselves, and in such patients, it is wise to enquire for a family history of allergy.. The question of a food allergy is much simpler to decide when blistering and swelling of the lips and mouth follow immediately on taking eggs or fish.

It sometimes happens that the sensitivity is not due to the taking of food at all, but to the handling of such food, as in the asthma of the housewife on handling flour.

The causative food may be an unusual or common article of diet, and the allergic response differs accordingly. In the instance of the former, the attack is usually short and abrupt, beginning with gastric symptoms, such as epigastric pain and vomiting, and later becoming colonic in nature, with diarrhoea. If a common article of food is the cause, the symptoms are generally chronic in type and continuous or remissive in

character, and they are usually colonic in origin.

It may be that the predominance of food allergy in children is predisposed to by overfeeding, the relative frequency of gastro-enteritis and the variability in the digestive secretions. One thing is certain and that is that it is rare to encounter a case of food allergy that did not begin in the first decade.

In infancy, the commonest sensitising agents are breast milk and cow's milk. In the former, the infant may be sensitive to one or other of the normal milk proteins, or to other proteins of the mother's diet that may be secreted in it. An interesting observation is made by Bray (118) that it is unnecessary to wean hypersensitive breast-fed babies if the mothers are given hydrochloric acid before the feeds; at any rate, he maintains the acid ought to be given to the babies.

It has been recorded above that, in children, dislike of a certain food may be of a protective nature. In later years, however, it is more often the taking of too large amount of a particular food that may precipitate an allergic attack. Moreover, the foods are ingested at a late hour, and there may be present chronic dyspepsia. Sometimes a food may be eaten cooked

when it cannot be taken in a raw state; and vice versa. For instance, sensitivity to the lactalbumen of milk may often be overcome by boiling the milk.

In allergic individuals, asthmatic attacks are particularly prone to follow late meals, heavy meals, bulky diets, or mixed cooking. Milk is regarded as being especially pernicious. Other articles of diet that frequently precipitate attacks are eggs, fried fish, tomatoes, bananas, strawberries and cocoa.

Reference has previously been made to Hurst's contention that big meals act in a reflex manner through gastric distension, the proof being that relief is obtained by vomiting. In like manner, the fact that defaecation may relieve an attack upholds the view that rectal distension may be a causal factor in other attacks.

Encouraging results have recently been obtained in America by Peshkin and Fineman (119) in the treatment of asthmatic children by altering the ketogenic-anti-ketogenic ratio of the diet. They have shown the value of a ketogenic and low carbohydrate diet in such children. These workers altered the ketogenic-anti-ketogenic ratio from a home one of 1:2 or 1:3 to 3:1 in a period

of three weeks, at the end of which time over ninety per cent of their patients showed moderate to marked improvement. It must of course not be overlooked that during this time foods to which such patients gave positive skin reaction were eliminated from their diet. At the end of ten months of such dietetic treatment over fifty per cent were considered moderately to markedly improved.

It is not always wise to place too much reliance on the history in patients with food allergy, as it is quite easy to blame the wrong article of the diet. Frequently the food to which the patient becomes sensitised is one that has been taken during a long and serious illness. Protein skin reactions are of great help in diagnosis, particularly in children; but in themselves they are not sufficient evidence of food allergy.

In 1928, Rowe (120) suggested the use of Elimination Diets. They exclude foods to which patients are most frequently sensitive - wheat and milk, egg, apple, banana, orange, celery, cabbage, cauliflower, potato, chocolate, fish and nuts. It is claimed that symptoms are relieved by the use of the correct diet in from five to fourteen days; if no relief is obtained at the end of such a period, other diets are tried.

All these facts suggest that food allergy certainly exists as a definite entity, giving rise to the various allergic syndromes, such as asthma.

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HEREDITARY PREDISPOSITION AND IDIOSYNCRASY.

The term "hereditary disease" is one which is often very loosely applied. In many instances it is not the disease which is inherited at all, but the predisposition to such a disease. Therefore it is necessary to abide by some strict definition in such a discussion as this. And it may be said that a disease is hereditary when it is transmitted as an integral part of the male or female germinal cells to the product of the union of these two cells. Such an inheritance is transmitted from one generation to another with a definiteness which is characteristic. Now in man there is no doubt whatsoever that a large percentage of cases of allergy show a definite familial taint; on the other hand, many patients with allergic disease have no such trait. So that the strict definition quoted above does not seem to apply to all diseases characterised by the phenomena of hypersensitiveness. Nevertheless, it is so usual to obtain a family history in which antecedents or contempories present allergic phenomena that there must be a definite predisposition to allergy in such a family. Various terms have been suggested from time to time to designate this predisposition.

Of these, there is one which is often used to define hereditary influences in other diseases, and which appears to be the most applicable in the diseases under discussion, that is "diathesis". By the use of this term, it is convenient to describe this marked tendency to inheritance in allergic diseases as the "Allergic diathesis".

It is obvious that "something" is inherited. As it is rare for a patient to manifest a hypersensitiveness to the same substances as his parents, it is not a specific hypersensitiveness towards a particular foreign substance or allergen. Furthermore the tendency to become sensitive is inherited from the father's side of the family as well as from the mother's. So that whatever is inherited must be a principle - a new reaction capacity, an "allergy" - and not a sensitiveness which is specific for the particular substance. Coca (65) and his associates incline to the view that a particular tissue or shock organ is inherited. The unstriped muscle in lower animals is such a tissue, and the varied sites of reaction in the different species depend upon anatomical peculiarities in the distribution of this muscle. In man, the muscular element of the blood capillaries has been suggested. The great difficulty

however, is to explain why one individual should develop asthma and another hay-fever, when they are both sensitive to the same substance.

Other authorities suggest the inheritance of an unstable vasomotor system. French authors postulate as an inheritance a specific bulbar centre, which is hyperexcitable to the effects of these allergic reactions. Many other theories have been advanced including, of course, endocrine dysfunction. The one characteristic about them is their vagueness.

Recent advances in biochemistry have stimulated the investigation of many diseases. It has been shown that allergic diseases have definite biochemical characteristics. And it does not appear at all improbable that the solution of what is inherited in allergy may be found in a further study of the biochemistry of allergy.

Whatever is inherited, transmission from parent to offspring takes place either through the placenta or through the germ plasm. Placental transmission is obviously not strictly hereditary owing to placental permeability. For it has been shown that in human beings only a single layer of cells separates the foetal from the maternal circulation, and that in such cases the placenta is

very permeable to the passage of various heterologous substances. On the other hand, transmission through the germ plasm constitutes true Mendelian inheritance, such inheritance being permanent in duration and capable of transmission to succeeding generations in definite numerical ratios. Obviously this kind of transmission is the only possible one from the father.

A true germinal herditary influence has not been shown to play any part in the anaphylactic reactions of animals. Up to the present, sensitivity has not been transmitted in animals from an affected male parent. So that the transmission commonly induced in animals is placental. Now sensitisation transmitted by way of the placenta to the offspring may be:-

1. Active - from the passage through the placenta of the sensitising agent (for example, serum) injected into the pregnant mother; as the amount of such agent reaching the foetus in this way must be small, such sensitisation is not very often observed; it is interesting to record that sensitivity may be absent at birth and develop days later in animals in which the sensitising agent is injected some time before birth:

2. Passive.- from the passage through the placental of maternal antibodies; this type of sensitivity is more easily induced and more frequent in occurrence; it lasts for about three months from birth.

The subject is much more complicated when applied to man. In the first place, sensitisation occurs in such varied types; the same cause may give rise to quite different types; and the same type may be due to quite different causes. Secondly, the behaviour of a subject of sensitisation is so unreliable; some may show no manifestations at all; in others, artificial sensitisation may be almost impossible. Thirdly, the difficulty of determining the mode of transmission is obvious. Transmission in man may, of course, be

(a) germinal or chromosomal, or

(b) placental.

Chromosomal.

Hereditary predisposition from the father may take place only in such a transmission as this. There has been much discussion about the manner of inheritance, whether as a dominant or recessive Mendelian factor. If the factor of inheritance is transmitted from parent to child as a dominant Mendelian characteristic, in a unilateral

inheritance fifty per cent of the offspring should be found sensitive, and in bilateral inheritance, seventy-five per cent; whereas in cases with no affected ancestry, the corresponding percentage should be nil. Should the factor of inheritance be transmitted from parent to child as a recessive Mendelian characteristic, comparable figures would be one hundred per cent in bilateral, fifty per cent. in unilateral and twenty-five per cent in patients with no affected ancestry. The earliest and most comprehensive study of this problem was made by Cooke and Van der Veer (66). On the whole the figures of these two observers approximate roughly those above, which are theoretical. They were:-

60 per cent in unilateral inheritance, and

67.5 per cent in bilateral.

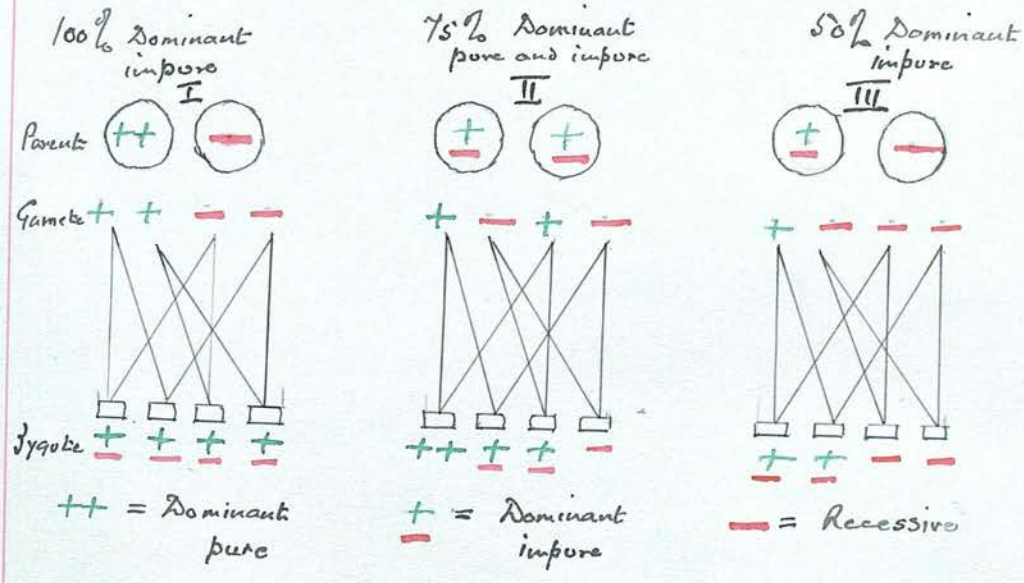
More recent information can be obtained from a study of nearly two thousand cases by Spain and Cooke (67), who give the following figures:-

58 per cent in unilateral inheritance.

69.4 per cent in bilateral inheritance

41.1 per cent in negative inheritance.

Clinically, no family of considerable size, in which every child was sensitive, seems to have been observed. So that if ever the dominant characteristic is pure it must indeed be rare. And the conditions of true chromosomal inheritance do not seem to be fulfilled in those affected with allergic disease.



SCHEME TO REPRESENT THE MECHANISM OF INHERITANCE

In patients in whom no family history is evident, the possibility of sensitisation taking place in utero must be remembered; in which case it is not absolutely essential for the mother to show any manifestation of allergy.

Placental. An interesting observation has been made by Ratner (68) on the inheritance of food allergy, which is that a mother's over-indulgence in certain foods of protein nature during gestation may lead to an active sensitisation in utero of the child; and the child after birth may show some allergic phenomenon as a result of coming into contact with such protein for the first time, although the mother did not manifest any sensitivity either before or during gestation. So it is evident that active sensitisation is brought about by the direct influence of the sensitising agent, transmitted through the placenta of the mother to the cells of the foetus. Passive sensitisation may be brought about by the passive transfer of antibodies from a sensitised mother; and the mother and child would then be expected to show the same sensitisation, which is not usually so. The observations of Cooke and Van der Veer (69) on this type of sensitisation may be summarised:-

there is no constant factor of sensitisation to be found in the offspring of maternal inheritance; the clinical form in such a child follows no definite lines, and may just as well be like that of the father as of the mother; in fact, it may even just as likely take the form to which a relative such as an uncle or an aunt is subject.

There thus seems to be some difference between anaphylaxis in animals and allergy in man so far as this hereditary factor is concerned. To substantiate this, it is as well to recall the following facts:-

passive sensitisation is the method usually discovered in animals;

active sensitisation in utero is difficult in animals but possible in man;

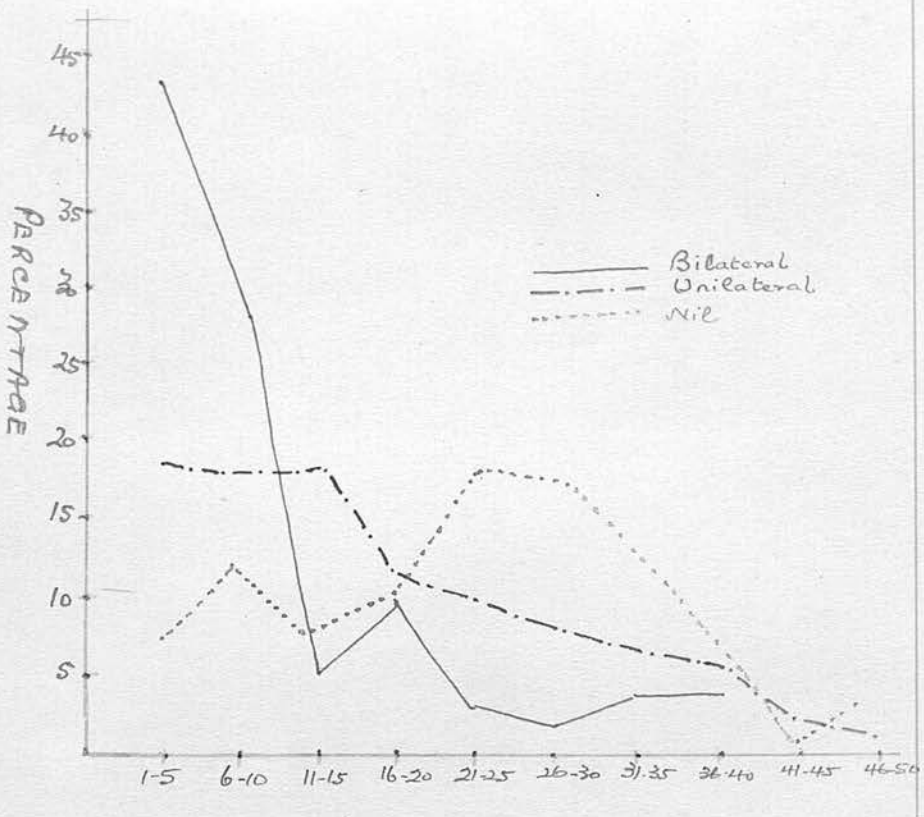
chromosomal transmission is frequent in man, but has not been reported in animals;

Inheritance determines not only the total incidence of hypersensitiveness; it determines also the age at which hypersensitiveness develops. It is generally agreed that the greater or more complete the inheritance the earlier the age at which symptoms will have their onset. Balyeat (70) finds that if the inheritance is unilateral, the

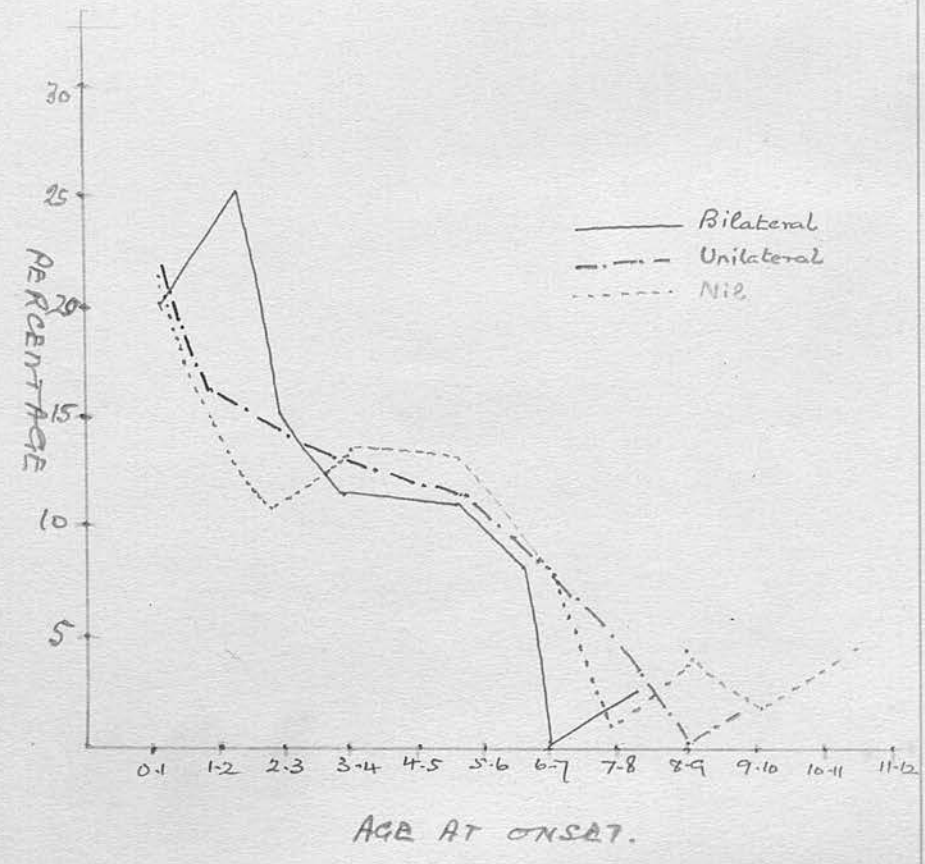
symptoms begin before the age of ten years in only thirty-three per cent; whereas if the inheritance is bilateral, the appearance of allergic manifestations occurs during the first decade in fifty-nine per cent of the parents. Cooke and Vander Veer's original figures support these findings (see page 236).

It is interesting to note that even during the first decade the incidence of inheritance plays a striking part. In those with negative inheritance, symptoms continue to develop up to puberty; whilst in cases with bilateral inheritance, practically all have developed symptoms before the sixth year. The figure on page 236 taken from Bray (71) illustrates this well.

Statistics suggest that puberty is probably the most important age in allergic individuals. Up to this age, a greater number of males than females is affected, and beyond this age the reverse is the case. Thus puberty appears to have some beneficial effect on males and a deleterious one on females.



Relationship of age at onset to type of family history.



Relationship of type of inheritance on the age at onset of symptoms.

The facts brought out by this discussion may be enumerated as follows:-

1. the majority of allergic individuals have one or more antecedents with some type of allergic manifestation, and a certain proportion of their children will develop symptoms; other children, though they may not show symptoms themselves, are capable of transmitting the tendency to allergic phenomena to their offspring;

2. two methods of inheritance are implicated, one of which, the placental, is not truly hereditary; so that whatever is transmitted cannot be explained satisfactorily by the Mendelian laws;

3. the greater or more complete the hereditary influence, the earlier the age at which symptoms will begin.

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TYPES OF ASTHMA.

Nothing perhaps is more convincing than clinical experience to uphold the view that asthma is not a disease per se but the term applied to express a group of clinical conditions, with an allergic basis. Such conditions occur in childhood and in adults; and there exists a marked contrast in them as a whole as seen at these two periods of life. Even in the child, however, there may be a variation in type, just as in the adult. The important point to be emphasized is that as age advances, so the type of asthma changes in detail. It is because this fact is not sufficiently recognised that many cases of asthma in childhood are overlooked. Indeed, it is too much a custom to withhold the diagnosis until the text book description of the clinical conditions as seen in the adult appears.

The outstanding difference in the attack as seen in the child and that in the adult is the preponderance in the former of symptoms of general intoxication. For the attack in the child usually lasts two to seven days, and is accompanied by general prostration, vomiting, headache and bowel disturbances. In other words, the paroxysmal

dyspnoea so characteristic of the attack in the adult, is, comparatively, an insignificant symptom. Moreover, the child usually recovers completely from an attack and remains free from further attacks for weeks or months. The case histories almost invariably show that predisposing causes in childhood are rich food, worry and excessive school work, and excitement.

As a contrast, the attack in the adult is generally attributed to climatic conditions, fatigue, and, to a less extent, dyspepsia. The predominant symptom is paroxysmal dyspnoea, which usually lasts a few minutes to a few hours, and is nocturnal in origin. This dyspnoea is accompanied by wheeziness and cough. Recovery is rarely complete, and over fifty per cent of patients complain of dyspnoea between the attacks.

It is perhaps convenient to consider asthmatic patients in four definite groups, two in the child and two in the adult. The characteristics of each group will now be considered.

Type 1. Childhood.

This is the child which is subject to attacks of asthma but otherwise appears normal. The story is usually one of asthma which occurs in

isolated attacks, frequently following a cold. A history of eczema in the past or present and a positive family history of allergy complete the picture. Except perhaps that the child may be slightly below the average weight, his general appearance suggests perfect health. About sixty per cent of this type show positive skin tests; and in most of these positive cases the tests agree with the history as to the cause of the trouble being extrinsic. No doubt in a few cases respiratory infections alone have precipitated the asthmatic attacks. Even more commonly perhaps the respiratory infections have lowered the resistance in some way to make a slight exposure to some foreign protein effective.

This type of case comprises about a third of the asthmatic children. The prognosis is usually good.

Type 2. Childhood.

In this, the symptoms are very much more obvious. The child is frail and tired-looking, with a thin delicate skin of rather pale colour and blue lips. The chest is characteristic with a prominent upper sternum and conspicuous dilated veins over its surface. There is a troublesome cough which often keeps the child awake at night; and wheezy

asthma separated by definite free intervals. As a type, it may be further subdivided into (a) a subtype, in which the definite free intervals are of considerable length, and (b) another, in which these intervals are of much shorter duration.

Subtype (a). In this type, the attacks are isolated simply because the exposure to the cause of the trouble is infrequent. For example, a considerable number have pollen asthma, with symptoms only during the summer months. In a few patients, the sensitivity exists for uncommon articles of diet. Also in this group are the few patients with simple bacterial asthma whose symptoms occur in typical attacks during the winter and spring, following colds. There is one peculiar and interesting type of case which must also be included in this group. This is the asthma which is associated with violent exercise and in which the patient complains of distressing wheezing whenever he plays, say, tennis. Such a patient is perfectly well otherwise. Altogether this group, which is twice as common in men as in women, amounts to about ten per cent of all asthmatics.

During the attack the physical signs are diffuse throughout the chest. Cough and sputum are generally absent during the attack, though a little

may occur at its termination. The complaint is generally of a mild dyspnoea with a musical chest. No evidence is obtained of a permanent change. X-rays of the thorax show nothing outstanding. There is, however, one point worth noting. Fully thirty per cent of these cases have a demonstrable focus of infection, usually in the paranasal sinuses and sometimes in the teeth as well. The interesting point is that such a focus does not appear to aggravate the asthma, and would seem to be unimportant. Therefore it is reasonable to assume that in this group some extrinsic factor produces a spasm of the smaller bronchioles.

Prognosis in this group obviously depends upon the nature of the allergen, and to a certain extent upon the treatment. It is not always easy to arrange changes of environment. So reliance must be placed upon specific treatment.

Subtype (b). Various etiological factors are at work in this sub-group, which comprises four main types of patient:-

1. those in whom symptoms are persistent, because the specific allergen is in continued operation;
2. those in whom the asthmatic symptoms are due to an extrinsic cause but which are being kept up by some secondary infection;

3. those who suffer from recurrent respiratory infections of asthmatic type;
4. those in whom a definite focus of infection serves to keep the asthma going.

It is to be noted that the patients of this subgroup are definitely free of symptoms between the asthmatic attacks. As a general type of asthmatic patient, it is common. To this group belongs the type of patients to whom the hospital is a boon, for he promptly recovers on admission owing to his having been removed from contact with the specific allergen. Another characteristic member of this group is the rather obese patient, women being in the majority. In these obese patients, in whom asthma is of fairly short duration, it will be found that the first attack definitely dates from some acute infection, such as pneumonia or influenza, and has occurred in attacks usually following "colds"; also these patients are worse in cold weather. This is "bacterial asthma". There is another type of obese patient in whom the asthma is of long duration, having started in the first or second decade; the original asthma had an extrinsic cause, and is now being kept up by a secondary infection.

So large is this subgroup that the prognosis may be taken as almost representing asthma as a whole. It is found that about fifteen per cent are "cured" and about forty per cent are "improved".

Type 2. Adults.

In this type, the patients have constant symptoms and no definite free intervals. It comprises two subtypes:-

(a) those without chronic bronchitis and emphysema;

(b) those with chronic pulmonary inflammation and distension.

Subtype (a). The distinction between this subtype and subtype (b) is probably artificial, as border line cases must occur; and no doubt emphysema occurs to a greater or less extent in all. Nevertheless a distinction as such is made because in this subtype (a) the patients do not have barrel-shpaed chests and the cough is relatively unimportant, with thin watery sputum of small amount. Breathing of various types may be encountered, but it is usually high-pitched and diminished. Similarly, the rales may vary considerably in quantity, character and distribution.

As a group, this subtype comprises about ten per cent of all asthmatics. It includes a type which is certainly most puzzling, in which

intercurrent infections, such as pneumonia and influenza, are accompanied by a complete disappearance of all symptoms for a time. Furthermore, treatment with vaccines and extracts of pollen, feathers and so on, to which positive skin tests are obtained, accomplish little. Many of these cases have eczema as well, The presence of two such allergic diseases together, combined with a positive family history of allergy and positive skin tests, strongly suggests some extrinsic factor as the cause; yet some other under-lying factor, the nature of which is unknown, must be at work, for the symptoms to persist and treatment to fail.

Another interesting type herein included is one which has given rise to much discussion. This is often referred to as "nervous asthma", the very contemplation of which is dangerous ground. For very often such simple procedures as change of residence may be followed by complete relief of symptoms. As discussed in the section on etiology, the nervous system of an asthmatic patient is subjected to great strain. Moreover, there does not seem any real reason why sympathy, interest, and suggestion should enter into treatment in this

disease any more than in any other. This type, at any rate, is found in middle aged, thin, tired men and women. The general health is poor, expression rather anxious, voice inclined to be nasal in quality, with lips and fingers somewhat cyanosed. They complain of indigestion, and any food is liable to aggravate the asthma. Although dyspnoea is obvious, cough is relatively unimportant; so the lesion is definitely spasmodic in nature.

There is also another type of case, practically only seen in women, in which the dyspeptic symptoms and obesity suggest gall-bladder disease. In such cases, although the symptoms appear to be severe and persistent, the patients remain well-nourished. Foci of infection in the nasal sinuses and teeth are frequently found. These patients are always short of breath and rarely sleep through the night. They complain of flatulent dyspepsia, often accompanied by epigastric pain.

An uncommon type of case, which belongs also to this subgroup, is one in which the onset frequently follows some severe nervous strain. Many of the so-called "war" cases are of this nature. The asthma is of very severe nature and treatment is most unsatisfactory. As a type, it has

characteristic features. The patient is thin and pale, restless, and appears uncomfortable. The physical signs in the chest are patchy and variable from day to day, with breathing which is diminished in intensity and high pitched in quality. The blood pressure is low, the pulse is rapid and of low tension, and sweating occurs easily. Obviously, the question of tuberculosis necessarily arises; and it behoves the physician to be on the constant look-out for its occurrence. For many maintain that the incidence of tuberculosis among asthmatic patients is considerably higher than among normal individuals.

Subtype (b). Very definite organic changes in the structure of the lungs and chest characterize this subtype. These patients have raised clavicles, stooped shoulders and barrel-shaped chests, which are hyper-resonant on percussion and in which the diaphragm is low. There is distressing dyspnoea and cough at night, with the expectoration of thick, yellow sputum, which may even be blood tinged. The percentage of these patients is in the neighbourhood of ten. There are two principal types. In the first, the patients are stout and plethoric in appearance, and have suffered from chronic bronchitis and emphysema for over ten years. Dyspnoea is obvious, and the voice is usually deep and rough.

The blood pressure is low and not what might be expected from the appearance of the patient. In only a few is it possible to trace a real progressive development and sequence of events from an attack of asthma, due in the first place to some such simple extrinsic factor as exposure to animals. In other patients, the persistence of a bacterial asthma may undoubtedly lead to secondary emphysema.

The second of the subtype is not very common. It consists mostly of men over fifty years of age, in whom symptoms have been present for only a few years. The onset of the dyspnoea is insidious, and there is no history of preceding asthma through early adult life. These patients are thin, with a voice which is nasal in type. The conjunctivae are suffused and the eyes puffy-looking. The cough is moderate in degree, with but little sputum. A characteristic feature is the general thoracic contour. The thorax seems to be more inflated than barrel-shaped, with the shoulders very high. When sitting, the position is erect with hands on knees and arms straight. In the X-ray photographs, the lungs appear very voluminous and the domes of the diaphragm are very low; but the heart appears normal in size and action. The

blood pressure is low, but arteriosclerosis is usually present. Paranasal sinusitis is the rule. Treatment is very unsatisfactory and so is of little value in helping towards an etiology which is unknown.

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ASTHMA AND X-RAYS.

X-rays are so universally employed at the present time that it is not surprising that use is also made of them in asthma. The all too prevalent tendency to diagnose by X-rays and to treat by X-rays can however hardly apply to this disease.

X-rays have been employed both in the diagnosis and treatment of asthma.

Diagnosis.

X-ray photographs are of course most useful for record purposes, but an examination should always entail screening as well. For the chest of an individual shows a different picture in inspiration from that seen in expiration. In the former, the ribs are separated more widely and the lung fields appear more luminous.

In asthma, X-rays depict the lungs as very distended, with ribs wide apart and diaphragm low, with flattened domes. The chest plate appears luminous. Indeed, the chest would seem to be "blown-up". This is the X-ray picture of emphysema. An important point to note is the expansion of the upper part of the chest; it appears square or with parallel sides, rather than

dome-shaped. Screening shows that the diaphragm has but little excursion during the breathing cycle. The flatness of the diaphragm, its relative immobility and the fixation of the chest in the expanded phase are really quite characteristic.

The X-rays are also useful in defining details of structure. Of these, one of the most obvious to be seen is the thickening of the peri-bronchial structures, with or without dense shadows due to lymph glands at the lung root. When these root shadows extend into the lung to a considerable extnet, the condition is referred to as pulmonary fibrosis. This peri-bronchial or pulmonary fibrosis is not uncommon. It would seem obvious to expect it in the more advanced cases of asthma. Nevertheless, cases of long standing asthma do occur without fibrosis, and fibrosis may be encountered in cases of only moderate severity. This X-ray appearance of fibrosis does not appear to be accompanied by any constant clinical sign or symptom.

Among other details of structure which may be met with in the X-ray photographs of asthmatic chests are the following:-

cardiac enlargement;

thickened pleura;

calcified glands;

unresolved pneumonia;

bronchiectasis;

excessive hilum shadows;

chronic bronchitis.

And yet, it must not be overlooked that in a large percentage of patients, the X-rays of the chest will show nothing abnormal. Some authroities maintain this to be so in thirty to forty per cent of patients.

In children X-rays of the chest are apt to be misleading. For even in children considered normal it is not uncommon to find some evidence of root or mediastinal shadows. Especially is this so in cases of asthma following whooping-cough and the exanthemata or associated with naso-pharyngeal infections. It is because of this tendency to dwell too much upon the presence of hilum shadows that most cases of asthma in children have been considered tuberculous.

X-rays can also bring to light other factors. For instance, they are of great value in excluding the presence of a foreign body in the chest, especially in children. Indeed, in any child with

asthma, in which the onset has been particularly severe, a special point should be made of having an X-ray photograph of the chest taken.

Treatment.

The clinical use of X-rays in the treatment of asthma is a recent development. It has been applied not only to the chest but to other regions, particularly the spleen, and in one instance to the pituitary. These organs were selected because of the theoretical possibility that their function influenced the production of antibodies. In 1927, Gerber (121) published a report in which he claimed partial or complete relief of asthmatic symptoms in seventy-five per cent of patients treated. His method was to apply treatment to the chest and also to the spleen. He maintained that X-rays produced four different effects:-

1. caused lymph nodes to shrink;
2. lowered the sensibility of the vagus fibres;
3. depressed the concentration of leucocytes and eosinophils;
4. stimulated the spleen to produce specific antibodies;

Waldbott (122) a year later, issued a report in which successes amounted to only forty-two per cent. In certain of his patients positive skin tests be-

came negative. He pointed out that the eosinophils were increased after treatment but decreased again later. He also drew attention to reactions of considerable severity which are liable to occur and which are characterised by vomiting and increased asthmatic symptoms. This radiation sickness has also been reported by Scott (123), who, however, claims good results from X-ray treatment in the large percentage of eighty. It is noteworthy that the number of successes claimed by each observer vary considerably. So that as a method of treatment it does not rest upon a very substantial basis. In general, it may be said that X-ray therapy may be expected to produce better results in children, particularly in those with enlarged bronchial glands.

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THE TREATMENT OF ASTHMA.

Asthma is a symptom of greater or lesser severity which occurs typically in attacks of longer or shorter duration. The patient may be found in a paroxysm of difficult breathing which will demand immediate symptomatic treatment. Unless the sufferer is comforted first, he has little interest or ability to answer any questions. Indeed, his condition may be very alarming. Such a state demands the exhibition of adrenalin, which has practically no contra-indications. On the other hand, the patient may seek advice between attacks to prevent further embarrassment. If the cause of the asthma can be identified, it can usually be removed. In about fifty per cent of patients, hypersensitiveness to some dust or food is present; and treatment consists in the elimination of or desensitisation to the specific substance. In another and smaller group the cause of asthma is a focus of infection which can be treated. There always remains however a considerable number of patients in whom the cause cannot be identified, or in whom asthma is due to acute or chronic infections of the respiratory tract which cannot be treated

specifically. Various methods of treatment will be discussed in order; some are simple and easy to carry out, others more difficult and require time and technical methods.

Whatever the special treatment is to be it is being planned for an individual who may take it easily and well, or who may react unfavourably to it. In a general way, something can always be done for every patient to make him more comfortable and to promote his general welfare.

The Immediate treatment of the attack.

A study of the foregoing subject matter demonstrates how very much the attack of asthma may vary in its severity. The first attack, if at all severe, is always terrifying. So the confirmed asthmatic, who is subject to frequent seizures, must be expected to be more tolerant of his burden. And indeed they usually are. In a previous section, attention was drawn to the effect produced on the nervous system by an attack of asthma. Confidence in the physician is a great factor in the treatment of disease, and in asthma particularly so. It is always dramatic to see a patient struggling for every breath relieved by the hypodermic administration of adrenalin. Within five minutes the change

in the patient's condition, mental as well as physical, is obvious. True it is that such a drama more often accompanies the earlier doses than it does the later ones given to a confirmed asthmatic, but the effect is almost always good. And yet it is by no means every patient that needs the hypodermic adrenalin. The ordinary asthmatic can usually move about, even though he be suffering with dyspnoea and some discomfort. In such a milder type of case, the burning of some kind of "asthma powder" may be alone sufficient to control the symptoms. The chief and customary ingredients of such powders are stramonium leaves and dry potassium nitrate, used in about equal parts. Cigarettes, composed of similar material, are often employed by others. The relief obtained by the use of such powders and cigarettes is due to the nitrites produced. These fumes are however very pungent and persistent, and consequently many now employ the more pleasanter pure amyl nitrite, a few drops inhaled from a handkerchief. It must be quite obvious that the inhalation of any pungent smoke is contraindicated in the type of asthma complicated by any infection of the bronchi. And yet it is extremely difficult at times to convince

asthmatic patients of the liability to further attacks such a procedure entails.

Another method of treating an attack is by the use of a nasal spray, containing cocaine (one per cent) and other drugs. Sometimes the 1:1,000 solution of adrenalin is used undiluted in a similar way and with good results. Convinced that the benefits derived from spa treatment are due to the inhalation of the vapours of the waters, Hurst (124) has advised the inhalation of carbon dioxide directly into the nose as a sedative, immediately an attack threatens. This may be done for five to ten minutes at a time. Time and experience teach each asthmatic patient in turn some ready way of relieving his attack. They go about consequently prepared and do not need the doctor. Sure enough the latter will be summoned should the attack prove more severe, and adrenalin will be called for.

Before proceeding to a detailed discussion of adrenalin, there are a few other points which are of some importance. Foremost of these is the necessity for warmth for the patient. How often does the doctor arrive to find a cold damp room with windows wide open, and it may be a gale blowing without; warmth is of paramount importance and

the patient must be kept covered. Asthma of any kind is extremely irritated by cold air, and particularly if there is present secondary bronchial infection. So whilst there must be plenty of fresh air, it must be warm and not cold. On finding a patient cold and clammy, much appreciation will follow the use of a hot foot bath. Always have the legs wrapped in a blanket. A measure which is often also most comforting is the rubbing of the back with or without a liniment. In these days when electricity is so widely used and so easily applicable, an electric pad applied to the back may be found very convenient.

Another point which needs emphasizing is that a patient in a very severe attack should be disturbed as little as possible. It is fortunate that the laity are always so confident that the attack in question will pass off. Deaths from asthma itself are certainly very rare; so that their faith is justified. It is obvious, however, that the right side of the heart has to undergo a great strain during an attack. So that the older the patient the greater the chance of a fatality occurring and the less should he be disturbed. The first duty of the

physician is to modify the attack, as by a dose of adrenalin. Then may he proceed with any examination he may deem necessary at the time.

Next, when an attack is severe and prolonged, feeding becomes a real difficulty. The constant effort to breathe makes eating and drinking difficult. In fact, it is not uncommon for a patient to begin a period of starvation immediately an attack sets in. Though the patient may do without food, it is essential for him to have fluids. It is advisable to try and get him to take four to five pints in the twenty-four hours. In the very severe cases with wizened appearance and dry and parched tongue and mouth, the fluid may have to be given in the form of salines per rectum with glucose added, or even in the form of subcutaneous salines. If asthma is due to a circulating toxin it is easy to explain the benefit when this toxin is diluted and excreted. In children, emetics are frequently of great service; but they may also be employed in patients of any age when there is marked abdominal distension. The benefit which they effect depends upon three factors:-

1. the relief of the distension of the stomach by vomiting;

2. the loosening of the mucous from the lungs, which accompanies a good emesis;

3. the sympathetic activity, as shown by the sweating, pallor, and rapid pulse and dilated pupils which precede the emesis.

Besides the simpler means of tickling the throat or drinking large quantities of salt and water or sodium bicarbonate and water, the following may be employed:-

Ipecacuanha wine in dose of ½ to ¾ oz.

Antimonial wine ½ oz.

Apomorphine hydrochloride 1/10 to 1/4 gr. orally, or 1/20 to 1/10 gr. hypodermically.

It is not unusual to find that a mother has caused her child to vomit to try and relieve the attack before calling in the doctor.

The bowels must be kept open in asthma as in other diseases. The difficulty of moving the patient makes enemata and defaecation a real problem. On the other hand, distension may be a problem of greater importance, and aperients or enemata may be of real value in the treatment. In chronic cases at least one bowel movement a day should be insisted upon.

If the patient is very exhausted stimulants are indicated. Of these strong coffee and hot alcohol are the best.

Adrenaline. The use of adrenaline in an acute attack is of such practical and theoretical importance that a thorough knowledge of its origin, action and dosage is essential. In 1855 Addison described a condition occurring in man which was characterised by extreme debility and apathy, associated with pigmentation; and which he considered to be due to tuberculosis of the suprarenal glands. In 1894, Schafer and Oliver found that doses of the extract of the suprarenal gland, when injected subcutaneously and intravenously into animals, produced a contraction of the blood vessels and a marked rise in blood pressure; and these same investigators later discovered that the blood pressure raising principle was contained in the medulla of the suprarenal gland. Various attempts to identify this active principle eventually culminated in the production of a crystalline compound by Takamine in 1901. To this the name of adrenalin was given.

Adrenal substance was first used in the treatment of asthma and hay-fever by Solis-Cohen, in 1898. He was himself a sufferer from these allergic conditions, for which he took, orally, tablets representing five grains of suprarenal substance, and the dose of which he gradually increased to ninety grains a day. Later, he

employed this treatment in his asthmatic patients. Though not universally successful, his results were such as to merit considerable attention. Many followed his example, also with varying results. In 1903, Ingals pointed out the blanching effect of a very dilute solution of adrenaline when used as a spray on the nasal mucous membrane. And in this same year adrenaline was first used subcutaneously in the treatment of asthma by Bullowa and Kaplan, with wonderful results.

Adrenaline acts by stimulating all sympathetic nerve endings. So it constricts the peripheral blood vessels and increases the blood pressure. It has no effect on the normal bronchi, but once constricted, as by pilocarpine or by an attack of asthma, it will cause vasodilatation. It overcomes the opposing parasympathetic or vagus action.

It is usually put up in solution; but may also be obtained in the form of tablets, which readily dissolve in water when needed. The solution turns brown when exposed to the air and loses its activity in a few days.

Adrenalin in its proper dosage, with its potency and immediate action, is of diagnostic importance. It is not at all uncommon to find the dose being used is unnecessarily large. Such a

large dose will often cause a train of disagreeable symptoms. These are important and should be carefully borne in mind. There is a sense of general weakness, with pallor and trembling. Beads of sweat appear. The pulse becomes rapid and the blood pressure rises. Such alarming symptoms may appear with great suddenness when adrenaline is injected intravenously. Fatalities have never, however, been reported. And the symptoms rarely persist beyond about fifteen minutes. They can be countered by giving histamine intravenously. All this serves to emphasize the importance of the dose, which seems to be so misunderstood. Small amounts, such as 0.25 c.c. of the 1:1,000 solution, are just as good as doses of four times the size. It is a well-recognised rough rule that the older the patient the greater the required dose. As is only to be expected, patients vary considerably in their reaction; but it is only very occasionally that one is encountered who is resistant to adrenaline. In children, it must be used with great care. Below the age of seven years, only small doses, such as 0.10 c.c. to 0.30 c.c. should be employed.

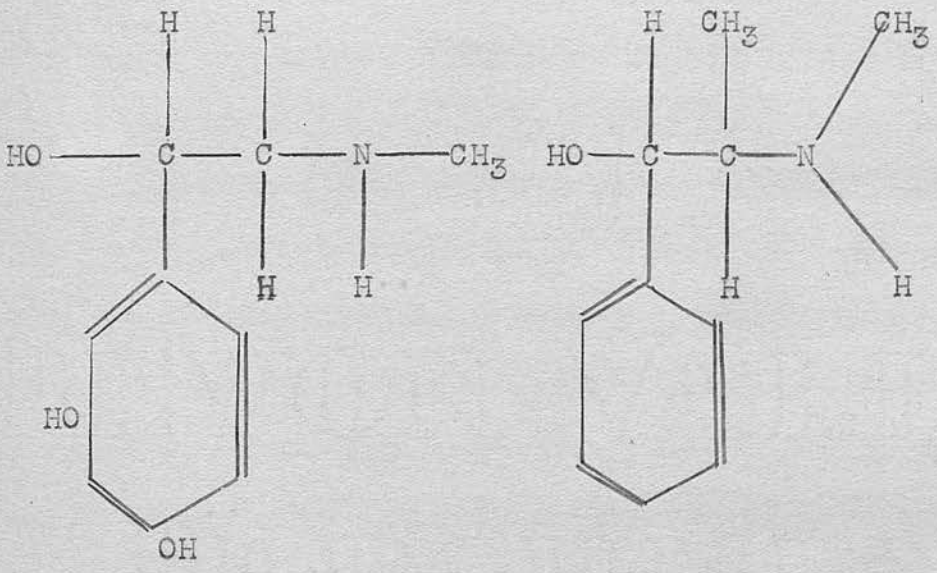
It is quite characteristic of adrenaline that tolerance is rarely attained by its use. In fact, most patients find it possible to reduce the dose

from time to time. Lilienthal (125) observed that when the effect of adrenaline has worn off, massage of the injected site may result in the relief of the asthma once more; and a single dose can in this way be made to last for several hours. Sometimes it is necessary to repeat the dose at frequent intervals for months at a time. The prolonged use of the substance in this way does not appear to lead to any organic change in the individual. To overcome the repeated injections in such patients, Hurst has advocated the continuous method of adrenaline injection; in this the needle of the syringe is kept constantly in position; after the initial injection of a dose that is known not to cause unpleasant symptoms, one or more minims are repeated every fifteen, thirty or sixty seconds, according to the patient's reaction, the rate being varied until it is found how frequently the injection can be made without any unpleasant symptoms arising; these injections may be continued for an hour or so; relief follows and is shown by the patient falling asleep.

Of recent years, there has come into use a drug derived from a Chinese plant, which has long been used in China as a circulatory stimulant.

The drug, called ephedrine, is the active principle of this plant, Mah Huang.

Ephedrine. The formula of this drug is quite similar to that of adrenaline, except that the ephedrine has an extra methyl radical and no phenolic hydroxy group.



Adrenaline Ephedrine.

Chen, Schmidt and Middleton (126) have reviewed the action of this drug with great care. They have shown that there is scarcely any respect in which the actions of ephedrine are identical with those of adrenaline. Ephedrine probably acts on the hypothetical myoneural junctions and thus produces its sympathomimetric effects. It also stimulates the central nervous system and depresses the action of the heart muscle.

The great advantage of ephedrine is that it

can be given by the mouth to have its required effects. Sometimes, however, it causes disagreeable symptoms, not unlike those following too strong a cup of coffee. These are sleeplessness, palpitation, sweating and a frequent inability to micturate. Ephedrine is readily absorbed and passes through the liver unchanged. The dose is 3/8 to 3/4 of a grain for an adult, three to four times a day; for children, it is 1/8 of a grain under one year, and 1/4 of a grain over one year. Patients taking the drug over long periods of time should be watched closely; for it has been reported when so taken as causing fatigue, weakness, restlessness, palpitation and tremors, associated with loss of weight, irregular swaying of the limbs in a more or less incoordinated manner. It is contra-indicated in acute circulatory collapse and cardiac disorders. Most observers agree that its chief use in asthma is as a prophylactic. For this purpose it may be given several hours beforehand to prevent an attack; or it may abort an attack if given during the prodromal period. It definitely is more effective in patients whose asthma is not complicated by secondary bronchial infections.

In conditions, other than asthma, ephedrine is

sometimes of great assistance. This is notably so in Hay-fever, given orally, and in urticaria, in which it frequently is most effecting in controlling the itching. The same may be said about eczema associated with much itching.

Whereas ephedrine has certain advantages over adrenaline, its action is much less certain and takes longer to be produced. The advantages are that it can be given by the mouth, is less rapidly destroyed by the tissues and so has a more prolonged action. Indeed, there would appear to be definite indications for the two substances, and one should not be allowed to take the place of the other.

Besides adrenaline and ephedrine, there are other medicinal agents which have been employed from time to time to relieve the asthmatic paroxysm. Of these, one has been very much used in America; this is Benzyl Benzoate. This drug has the same effects on smooth muscle tissue as papaverine, the alkaloid of opium, but without the narcotic effects. It is certainly metabolized in the body and has a comparatively low toxicity. On account of its action in controlling smooth muscle, especially in the bronchi and intestines, it was recommended for use in asthma, hiccough and so forth. The results

are on the whole very disappointing in asthma. Nevertheless on occasions it is exceedingly prompt, and efficacious in its effects, and it is certainly worth a trial in any refractory case of asthma, particularly in children. The dose is half a teaspoonful of the twenty per cent solution in ethyl alcohol

The next is Atropine. If the bronchial spasm is produced by vagal stimulation, then atropine would be expected to cut short the spasm and so stop the attack of asthma. As a matter of fact, it is very rarely effective, and may produce alarming symptoms.

Morphine does not relieve bronchospasm. It acts only as a general depressant. It should be used in asthma as a last resort only; for this is a chronic and distressing disease in which a drug habit is only too easily developed. There is, however, one condition which may simulate asthma very closely and in which morphine is definitely indicated. This is cardiac asthma, in which morphine is the very best treatment.

The use of the substances so far discussed is

not confined to the treatment of asthma alone. They are of particular value in the immediate relief of any manifestation of allergy, such as hay-fever, urticaria, and so on. It is always important to bear in mind that the relief obtained in stopping an acute attack is of very great value to the general health of the patient. Indeed, such relief enables him to improve his general health and so to control the underlying disease.

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THE TREATMENT OF THE FUNDAMENTAL CAUSE.

The attack of asthma having been relieved, effort must then be made to establish and overcome the underlying cause. So that really the treatment of the fundamental cause must begin with an accurate diagnosis. In many cases this may be simple, in others obscure and very difficult. Always there remains a large group of patients in whom no precise cause can be identified. Again, there is the group in which the original asthma had a simple beginning but is now complicated by secondary infections. Such cases call for symptomatic treatment, in which drugs will play their part.

Drugs. Of all the drugs used in asthma there is one which has well stood the test of time. This is Potassium Iodide. It has been aptly termed the "sheet anchor" of treatment in asthma. The type of patient in whom the iodide is particularly suitable is that in which asthma is complicated by secondary bronchial infections. These are the patients who complain of a sense of tightness in the chest, in whom small, crackling rales are heard all over the chest and in whom cough is very troublesome. Whether the iodide actually

relaxes the bronchial spasm, or whether its effect is solely to dilute the bronchial secretion and enable the patient to raise it with greater ease, is doubtful. At any rate so great is the belief in iodides and so reliable its effects that most of the proprietary medicines used in asthma have it for their base. Many clinicians use sodium iodide as a routine in preference to the potassium salt. It is said that the corresponding salt is less injurious to the body.

The dose of iodide used should be five to ten grains, two or three times a day. Larger doses will achieve no more. Patients vary considerably in their ability to take the drug. It may give rise to a bad taste in the mouth and vague discomfort in the epigastrium, accompanied by flatulence. Large doses will also produce an acneform rash over the chest and back. In some patients, the iodide alters the sputum to such an extent that the cough is made worse. In such cases, by stopping the drug, the cough and bronchial secretion may disappear altogether.

The iodide is often combined with Belladonna; and it is claimed that better results are obtained than if either is given independently. However

true this may be, it seems illogical to combine thus a stimulant and a depressant of the mucous glands.

There is certainly one drug which can be most usefully combined with the iodides in a certain type of patient. Such is Arsenic, which helps to improve the general condition. Such a combination is especially beneficial in children, suffering from chronic asthma and bronchitis and living in unhygienic and thoroughly unsuitable surroundings.

There remains to be discussed one other drug which is a great use in many allergic conditions - that is the Salicylates. It has been shown by Swift (127) and his co-workers that anti-rheumatic drugs inhibit the concentration of circulating antibodies. When sodium salicylate was added to living and dead cultures of streptococci, and the mixture injected into animals, the production of complement-fixing bodies, of agglutinins and of haemolysins was much smaller than in the control animals. They therefore believed that the beneficial effect of salicylates was due to this effect on antibody production. No study of this action of salicylates in asthma has been made. Nevertheless, decisive benefit frequently follows their administration. Two forms of the drug are usually employed, viz. sodium salicylate and

aspirin. Either may be given to abort an attack in its very early stages; and often five to ten grains of aspirin taken at bedtime will keep a patient free from asthma during the night. On the other hand, a hypersensitiveness to aspirin is not uncommon; so that the first dose of either salicylate or aspirin should be given cautiously.

Endocrine and Organic Extract Therapy.

This has received a good trial in asthma. The results entirely depend on the existance of a complicating endocrine disease. There is, however, one type of case in which good results are reported from time to time both in physical condition and in the diathesis. The type referred to is the fat boy, with large breasts and hips suggesting a female, who has sparse fine hair in the axillae and pubes, and whose genitals are poorly developed. These boys seem to be subject to asthma very often. The employment of anterior pituitary substance may lead not only to remarkable improvement in physical appearance but also to a disappearance of the asthma.

Blood Therapy. The use of whole blood or its constituents in allergic conditions followed the elaboration of an interesting idea by Kahn and Einsheiner (128) in 1916. They contended that in

asthma the circulating blood contained a "poison antigen", that repeated doses of antigen desensitise, and that therefore injections of the patient's own blood ought to contain this antigen and thus desensitise the patient. The blood, withdrawn from the patient, was whipped, the clot removed and the plasma filtered. Subcutaneous injections of this defibrinated blood plasma were given in doses of 5.0 to 10.0 c.c. It is to be noted that the withdrawal of the blood and its preparation for use in treatment necessarily alters it in many ways. So that its reinjection must inevitably simulate an injection of a foreign substance. In other words, the mechanism must be non-specific in its fundamental aspects. At any rate, the use of this autogenous defibrinated blood has definitely proved of value in urticaria and angioneurotic oedema. In asthma, the response may be immediate and the attacks may cease for months. It is however, only an occasional case in which it appears to have any definite effect. The author has been using whole blood injections in doses of 5 to 20 c.c. in allergic conditions. The blood is withdrawn from a vein and before it has had time to coagulate, it is injected deep into the

buttocks. The results in urticaria have been excellent in the few cases treated. In asthma, ten cases have been so treated. Four of these were patients with definite allergic asthma; in the other six, a secondary bronchial infection was present. The results in the former were exceedingly promising. In three of the four, the blood injections were carried out half-an-hour after an injection of 0.25 c.c. of adrenalin; and in these cases, the attacks cleared up without any further treatment. In the fourth patient, the blood was withdrawn into a syringe already containing the adrenalin; this combination of blood and adrenalin was thus given at one and the same time. This patient was also thus freed of the attack. In these clear-cut allergic patients, the only other treatment adopted at the time was their removal to another room in the house. One was a child, aged 4; in him milk was at the same time omitted from the diet. The point to be emphasized is that in these patients, it was not found necessary to employ the usual drug treatment - potassium iodide and so on - to hasten the period of recovery from an attack. So that the injections not only aborted

the attacks, but definitely shortened the period of immediate convalescence from them, also.

In the patients, in whom bronchial complications existed, the results have not been so satisfactory. Indeed, adrenalin seemed more effective, during an attack, when given alone than when combined with blood. The blood by itself, however, seemed to make the patient more comfortable, but did not abort the attack completely. In one way, however, even in these patients, these blood injections have proved of definite value. This is in the ultimate improvement in the general health. This has been achieved by continuing the injections once weekly for periods up to three months.

Whereas it is obviously unwise to draw any conclusions from such a limited number of patients treated, any observations must be of value in a disease in which the results of treatment are so varied. And the results above warrant the contention that the use of whole blood injections has a definite place in the therapeutics of uncomplicated allergic asthma, and that they are even of value in patients with bronchial complications in so far as the general health is very much improved by their use.

Another method of employing blood has been

suggested in the use of autogenous serum. The patient's blood is allowed to clot and doses of the freshly prepared serum are given intramuscularly in amounts of from two to ten c.c. at intervals of two to seven days.

In 1927, McBroom (129), reported five patients with severe asthma in whom blood transfusions from healthy adults were carried out. His results were definitely encouraging. Such a method might be expected to neutralize any toxic product responsible for the attack, as well as to stimulate a resistance to it in some non-specific manner.

Desensitisation.

The principle underlying desensitisation consists in applying just enough stimulus by some allergen or other substance to use up the reactivity or reduce or exhaust the cellular allergin. Specific desensitisation is the term employed when the definite causative allergen is used; Where there are multiple reactions, the largest of each group may be combined. The methods of desensitisation include - a series of doses which are ordinarily given by subcutaneous injections; next, feeding the specific substance in small but increasing quantities may be of great value, particularly when the allergen is a common food; thirdly, in dust or pollen

allergy, repeated cutaneous reactions may be made use of for the purpose of desensitisation.

Desensitisation may also be carried out prophylactically, when the doses are given well in advance of the expected time of exposure.

Subcutaneous desensitisation. This, the commonest method adopted, is chiefly of use in patients with epidermal and pollen hypersensitivity. There are two ways of carrying it out. (a) the "rush", and (b) the lengthy weekly. A series of dilutions of the offending substance or substances is prepared. The size of the initial dose is based upon the tolerance, which is arrived at by making skin tests with the various dilutions. The number of doses and the interval between them cannot be determined in advance but will depend upon progress. The usual practice in the lengthy method is to give injections every five to seven days, the interval depending partly upon the size of the local reaction produced by the previous inoculation. The local reaction also determines the strength of the succeeding dose; if this is small, the next dose may be double the strength of the previous one. The doses should be continued either until the patient is greatly improved, when the intervals between doses may be gradually lengthened out to four weeks apart, or until the

dose reached is such a size that the patient's tolerance to subcutaneous treatment is obviously at a much higher level. If symptoms continue, despite this high level, further doses are not worth while. The "rush" method is used in patients having frequent and severe attacks or in those kept in intimate association with the specific allergen. The injections are given at two-hourly intervals each day until in five to seven days the patient can stand large doses of a maximum strength with impunity.

Ingestion desensitisation. Daily doses of the food or specific peptone derived from it are employed, commencing with small amounts and increasing very slowly. The time taken for desensitisation depends upon the size of the initial amount that can be ingested without symptoms.

Perennial treatment in which a dose of the specific allergen is given once a month throughout the year is sometimes employed.

The skin tests made at the end of treatment vary. In some instances, they may be negative, in others the same size as before treatment, and in others even larger. The end results as found are not parallel with or dependent upon such a desensitisation as would be indicated by a diminishing skin reaction.

General reactions to desensitisation treatment are important and may be serious. The symptoms are always dramatic, severity and prompt appearance being characteristics. Coryza, urticaria and asthma are the usual manifestations; but collapse as in an acute abdominal emergency has been observed. The prompt use of adrenalin abolishes these reactions, fortunately.

Many patients discover that they can take certain foods when cooked which lead to reactions when ingested in the raw state. The changes effected by cooking and preparation are referred to under the term denaturisation.

Protein shock therapy. This non-specific therapy may be described as the parenteral introduction into the organism of agents which bring about a reaction or disturbance which affects the disease process. To obtain this effect, any foreign substance may be used. The reaction which follows the parenteral injection of salt solution, of drugs, or protein substances of various complexity and structure, may in each case be described as non-specific. The foreign substance may be injected intradermally, subcutaneously or intravenously, and in each instance the reaction

will be somewhat different. The subcutaneous injection of typhoid vaccine produces redness and swelling at the site of the injection, which appears in from twelve to twenty-four hours and which may last for two or three days. This local reaction is the important feature. On the other hand, an intravenous injection of this typhoid vaccine or some foreign substance like peptone is followed within a few minutes up to an hour or two by a general reaction; in this, the patient feels flushed and uncomfortable and experiences a chill with the temperature rising, perhaps, as high as 103°F. There may be violent rigors; and he feels ill for a day or two. This general reaction is the object of the treatment.

This method of treatment is supposed to result in the stimulation of the cells of the organism. As a result of this there is a greater production of specific substances, antibacterial substances especially, and an increase in the speed of detoxication. At the same time, it has been observed that the body metabolism is notably increased, particularly the carbohydrate. So that the patient feels better.

Non-specific agents have a definite effect upon the permeability of blood vessels and, therefore

on inflammatory processes. It was pointed out in a previous section that a non-specific serum could displace the antibodies in an animal sensitised to other serum. It is possible that vaccines can in a similar way displace similar antibodies and thus bring about a degree of desensitisation. Again, in a previous section, attention was drawn to the characteristic feature of bacterial allergy, namely, that the specific skin reaction was delayed in appearance, inflammatory in nature, and often severe in degree. It was particularly noted that this reaction occurred only in tissue disturbances. In other words, the question of a hypothetical "third substance" was raised. It is through the action of this third substance that the tissues are prepared to make the animal hypersensitive.

There are two noteworthy facts which justify the use of non-specific protein therapy in asthma and allied allergic states. First, very definite relief of symptoms is often obtained by vaccine treatment. Secondly, the relief of allergic symptoms which accompanies acute infections is always striking. Asthma, hay-fever and urticaria all clear up when fever occurs from any cause. Many substances have been in turn recommended to produce the required effects. Of these, peptone was one

of the first. It was used by Auld (130) as an intravenous injection, in a five per cent. solution, given every three to four days in doses of 0.30 c.c. to 1.30 c.c. Temporary benefit in asthma and vasomotor rhinitis is said by Vallery-Radot (131), to have followed the oral administration of 0.35 gm. of peptone, one hour before meals. The object of the latter was to produce a larger contact with the allergen. More recent investigators, such as Ramirez (132), maintain that peptone is of no value in the treatment of bronchial asthma.

Another substance that has been recommended for use in this kind of therapy of milk. Its chief exponent has been Schiff (133), who pointed out that there was a ready supply and that preparation was simple. Two ounces of whole milk were put into a rubber capped bottle and placed in boiling water for one hour. He gave three doses a week, beginning with 0.50 c.c. and increasing by 0.50 c.c. to a final dose of 3.0 c.c. He did not achieve as good results with this form of treatment as he did with specific desensitisation or non-specific peptone therapy.

Vaccines and Tuberculin.

This is a subject in which a vast amount of

experimental work has been done. Vaccines may be expected to act in one or both of two ways. The first is the induction of a specific impunity, directed toward the particular organism used in the vaccine. Secondly, the non-specific local delayed reaction may in itself be responsible for any benefits derived from the use of the vaccine. It is a well recognised fact that the production of a definite local reaction in the subcutaneous tissue as a result of the injection of the vaccine, may be taken to imply that the use of such a vaccine will be of definite benefit. This local reaction does not appear at once; instead, a red swollen inflammatory area, deep in the tissue, is seen to develop in about twelve hours. It is decidedly tender and may persist for several days.

Both autogenous and stock, or non-specific, vaccines have been variously employed. Most observers, perhaps, have used the former, the predominating organism being a variety of streptococcus. On the other hand, Rackemann and Graham (134) have noted very little difference in the end results obtained with the two types of vaccine. They maintain that the production of the local delayed reaction, mentioned above, is essential for success in treatment. So that they would place

more reliance in vaccine treatment upon the non-specific effect. They support their contention by pointing out that almost identical results are obtained with either type of vaccine, as stated above. If this is so, it may be that the local reaction from the dose of vaccine results in the production of a poison comparable to the hypothetical "third substance".

There being thus different ideas as to how vaccine therapy accomplishes its object, it is necessary to discuss the preparation of the vaccine. The most obvious source of the organism is the sputum. It is usual for a vaccine, containing more than one organism, to be made from such a source. In 1920, Rackemann (135) described the technique of isolating single organisms from the sputum and making separate vaccines for each. Famulener (136), advises routine cultures from various foci, including the respiratory, digestive and genito-urinary tracts. Whatever the source, the organisms are grown on slants of some solid medium, such as plain agar or human blood agar. In view of Rackemann's theory, it seems advisable to retain the bacterial bodies and their extractives in toto. The growths on the media should therefore be washed off with salt

solution and used in the original suspension. An intradermal test is made with the vaccine thus obtained, and, if positive, dilutions are made for therapeutic purposes. It so happens, however, that positive test reactions are obtained almost as often with stock vaccines. Indeed, vaccines containing any gram-negative organisms appear to produce such a reaction almost universally. This has led Rackemann to suggest the use of two vaccines simultaneously; should a local reaction be produced by either, that concerned is used for treatment; and if no reaction follows both, another vaccine is employed; or, in the case of an autogenous vaccine, a larger dose is injected. More recently, the same observer has advised treatment with two vaccines at once, injected into separate places, regulating the dose of the one quite independently of the dose of the other, the object being in each case to produce a small local inflammatory reaction.

There is no doubt that this subject has been taken a stage further by the significant work of Knott and his associates (137). They have found gram-negative bacilli in 36 per cent. of the sputa of asthmatic patients; and in seven-eighths,

of the cases in which these organisms were found, the sputum was eosinophilic. Skin tests made with emulsions of these organisms gave positive results, in 74 per cent. of the patients from whom they were isolated, and in only 11 per cent. of the patients in whom they were absent. They conclude that these bacilli belong to the B. Friedlander group. It is suggested that these organisms might in asthmatics be producing histamine actually within the bronchioles. Evidence is already forthcoming that many of these bacilli are histamine producers. Vaccine treatment with gram-negative bacilli from the sputum has been carried out in eighteen patients; in seven, this has been unsuccessful, whilst three patients were cured and eight improved.

Whatever vaccine is employed, some mild local reaction should follow its use. There is no doubt that success in the vaccine treatment of asthma and allergic states runs parallel with the production of such local reaction. The size of the doses varies naturally with this local response. When this is definite, increases in dosage are made slowly. Should no local reaction follow a dose, the next to be given can be double the last. And if no reaction follows the dose of

1.00 c.c. which usually represents about a billion organisms, such vaccine should be given up for that patient. The interval between doses is four to seven days, the earlier ones being given at shorter intervals than the later.

It is uncommon for general systemic reactions to follow ordinary subcutaneous doses of vaccines. Serious and fatal accidents have been reported. They usually have, however, followed the use of vaccines intravenously or some obvious contra-indication, such as pyrexia. There is no doubt that asthma can be aggravated by vaccines. Such a happening indicates two things:-

(a) that the vaccine used is effective;

(b) that the dose is excessive.

Further management of such a patient consists in omitting the next dose or two entirely, and then beginning at one-half the dose that caused the exaggeration of the asthmatic syndrome.

If the vaccine is likely to result in any pronounced improvement, such will be observed to occur after the first few doses. Indefinite prolongation of treatment for weeks does not seem to increase the original improvement. There are, however, exceptions to this statement.

Many patients themselves maintain that vaccine treatment has been their saviour. In such instances, it is customary in some clinics for these patients to continue having monthly doses of the successful vaccine over considerable periods of time.

There are certain definite comtra-indications to vaccine therapy. The first is the presence of fever. Therefore in all acute conditions, vaccines should be employed with great care. Secondly, it is unwise to give vaccines during an acute asthmatical attack. Thirdly, there is a type of patient who is sensitive to vaccines of all kinds and in whom the minutest dose is liable to produce alarming reactions.

Whereas many authors maintain that vaccines do good in asthma, it cannot be said that they have proved of any permanent therapeutic value. For symptoms frequently return when the vaccine therapy is terminated.

Tuberculin therapy. Patients afflicted with asthma have no doubt been subjected to the tuberculin test to a greater extent than in any other disease. The frequency of positive reactions, however, prompted the use of tuberculin as a non-specific method of treatment. It was introduced by Van Leeuwen and Varekamp (138), who issued comprehensive reports in 1921 and 1922. The percentage

cured or greatly improved was indeed high. Such results have not, however, been obtained by any other observers. Therefore it is necessary to point out that the high percentage of successes claimed by the former two observers must, in great measure, be due to the conditions under which the treatment was carried out, namely, the stay in hospital associated with a change in the activity of the patient. On the other hand, it is of interest to note that attacks of asthma were produced by the treatment in at least two instances. Local reactions following the subcutaneous doses seemed to be important for success. In fact, any improvement does not appear to be in any way different from that effected by most ordinary vaccines.

The method of treatment is to commence with minute doses, such as 1/10 c.c. of a one in one million solution. Such an injection is given daily or at two-day intervals until either all the symptoms of allergy have disappeared or there is a strong local reaction or a general reaction. In the latter contingencies, the dose is kept fixed at the quantity last given, and the frequency is diminished to twice a week, once a week, and then

once a fortnight. Should allergic symptoms re-appear after treatment, the same method is repeated.

Active tuberculosis is, or course, a definite contra-indication to treatment on these lines.

Physical Therapy.

The use of X-rays in the treatment of asthma has been considered in a previous section. It need only be reiterated that the results are very unreliable.

Actino-therapy. Ultra violet ray irradiation has been recommended especially in children and particularly when the X-rays show large tracheo-bronchial lymph nodes. There is difference of opinion as to results obtained by this form of treatment. Many, including the writer, consider that ultra-violet irradiation often makes the attacks of asthma worse. The rays are applied locally to the chest and generally to the body and limbs. The usual source of the rays is the quartz mercury vapour lamp. The initial dose should be one to two minutes at a distance of three feet. The amount is gradually increased at bi-weekly attendances. The course of treatment should not exceed three months. Generally, it may be said that, though in a few cases it may have a slight

sedative and tonic action, it does not affect asthma directly.

Galvanisation, faradisation and diathermy all have their advocates. Suffice it to say that the mere fact that they are not in general use for the treatment of asthma speaks for itself.

Bronchoscopy. As a form of treatment, this has received much more attention in America than in this country. It has received a great impetus from the work of Chevalier Jackson. It is claimed that the best results are obtained in those patients who have a chronic infection of the trachea and bronchi, with increased secretion. It is also maintained that vaccines made from organisms cultured directly from the bronchial secretion are much more effective than other vaccines made from the organisms of the sputum. The limited use of this form of treatment renders it difficult to offer criticism. Bronchoscopy may be used:-

1. to remove excessive bronchial secretion;
2. to apply drugs directly to the bronchial mucous membrane.

In the first it is chiefly of use where the secretion is so sticky and tenacious that the patient cannot easily raise it by coughing or

where iodide fails to loosen it. The removal of such secretion will be followed by clinical improvement which may last for some weeks. At best, however, the improvement is only temporary and the asthma tends to return. The second object of bronchoscopy, namely the local application of drugs, has on occasion provided definite relief from the asthmatic attack. Cocain, silver nitrate and iodine have all been used. More recently, lipiodol and gomenol, an essential oil extracted from a plant grown in New Caledonia, have been tried. It is claimed that the relief obtained may last for months.

As an alternative to bronchoscopy, the latter two preparations are sometimes injected through the crico-thyroid membrane into the trachea. Treatment of asthma in this way is, however, new and its limitations remain to be determined.

Surgery.

The nerve supply of the heart and lungs is very similar. And as operations for severing the cervical sympathetic or vagus nerves have been devised in the treatment of angina pectoria, so many surgeons have attempted to apply similar operations in that of asthma.

The anatomy of these nerves is most important and must be considered in detail. The sympathetic trunk arises from the jugular foramen and descends downwards close to the spine. It lies deep in the neck, beside the vagus nerve. At its upper extremity it broadens out into what is known as the superior cervical ganglion. From this ganglion, grey rami are given off to supply the peripheral structures of the face and head. About the level of the fourth cervical vertebra, there is another enlargement known as the middle cervical ganglion, likewise giving off grey rami. Still lower, is another ganglion, known as the inferior cervical. This lies in close relation to the vertebral artery, near its origin from the subclavian. Near the inferior cervical ganglion is another small ganglion, called the first dorsal. As a matter of fact, these two are very commonly fused together. At any rate, they are considered together as the stellate ganglion, a very important structure. Above it, the cervical sympathetic has no connection with the spinal cord. Afferent impulses which originate in the head, or in the nose and throat, must descend to the stellate ganglion before crossing to the cord and ascending it. Impulses from the heart and lungs follow a similar route because both these organs have

direct connection, through sympathetic fibres, with the cervical ganglion. At and below the stellate ganglion, however, white rami connect the sympathetic chain with the cord at each segment. It has been shown that the heart is also connected to several of the dorsal sympathetic ganglia by grey rami and is not denervated completely until these dorsal connections have been severed. Similar important connections have been proved to exist between these ganglia and the lungs.

A consideration of this outline of the anatomy clearly demonstrates that operations that affect only the superior and middle cervical ganglia and the entire sympathetic trunk with the stellate ganglion must of necessity be only partially successful. For impulses from the heart can still cross directly to the second, third and fourth thoracic ganglia to enter the cord at this level. So to block these impulses as well, their paths must also be included in the operation.

Most operative work has been done on the sympathetic. The surgeons maintain that the fibres of the sympathetic and of the vagus were in close anatomical and physiological association throughout their course, and particularly below the stellate ganglion.

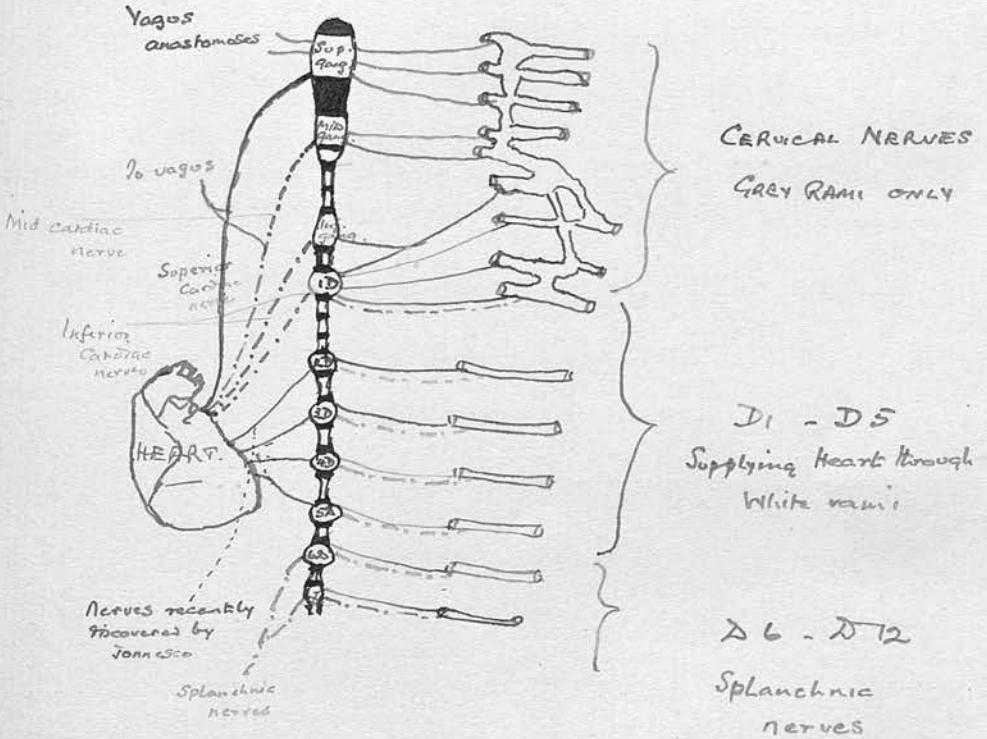

DIAGRAM OF SYMPATHETIC NERVOUS SYSTEM
IN CERVICAL AND DORSAL REGIONS

For bronchial spasm ought, theoretically, to be a vagus rather than a sympathetic effect. At any rate, operations on either the sympathetic or the vagus have been followed by only very temporary improvement; and, as it has been practised, sympathectomy can be regarded as of no value in the treatment of asthma.

The proximity of the sympathetic trunks and ganglia to the bodies of the cervical and throacic vertebrae would seem to render them vulnerable to regional anaesthesia. A technique has been suggested in which the needle is introduced between the ribs and then turned medially to strike the side of the body of the vertebrae; so that when an injection is now made the fluid is brought into close contact with the nerve concerned. If novocaine is used, its effect on the nerve is at once apparent by the occurrence of:-

1. flushing of the face;
2. contraction of the pupil;
3. narrowing of the palpebral fissure;
4. enopthalmos, all on the same side.

Moreover, the pain of angina pectoris is immediately stopped. When the location of the needle point is proved in this way by novocaine, the injection of alcohol to destroy the nerve can

be easily and safely made, or better, surgical extirpation can be considered. Such a method seems to offer a real approach to the dorsal ganglia, and is essentially free from danger.

Nasopharyngeal surgery. The scope of nasal operations has been a most debatable point. Submucous resection should be performed only in those cases in which nasal obstruction is evident, both subjectively and objectively. The removal of a simple septal spur, in the belief that it may be causing irritation resulting in reflex asthma, is not justifiable. Every conservative effort should be made to retain the turbinals on account of their function of warming and moistening the inspired air. Polypi must be removed. In the milder forms of hyperplastic conditions the area of hyper-plasia should be removed as far as possible, and local treatments instituted. In the milder types of localized infection, conservative treatment is justified. Where there is excessive muco-purulent secretion, the Dowling pack of ten per cent argyrol solution should be employed; these packs are left in position for half to one hour and then removed, and are repeated every few days or so depending on the indications. In many of the patients, however, the extent of the pathological lesions is striking; and

in such cases attempts at conservative treatment are likely to fail. So extreme radical measures may have to be adopted, consisting of the complete removal of all the lining membrane of the antrum and as complete a clearing out of the ethmoid as possible. Unfortunately, such procedures do not have much effect on the course of the asthma. When it is realized that the ethmoid labyrinth may have prolongations over the orbital roof and posteriorly to the outer side of the sphenoid, it is obvious how extremely difficult it is to effect complete eradication of chronic infection from the accessory nasal sinuses. In conclusion, operation should be advised only in patients in whom the lesion in the nasopharynx is well enough defined to demand treatment for itself, without regard to the asthma. Such treatment may relieve the asthma; at any rate, the patient as a whole will be improved.

Cauterisation of the nasal septum has been advised the idea being to dull the receptive area in the nose, where irritative stimuli may lead to the naso-pulmonary reflex. Such a procedure must obviously be only a temporary measure, so far as improvement is to be expected. It is useless without the recognition and treatment of the underlying allergic state.

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RECENT ADVANCES IN TREATMENT.

Glucose. As biochemical investigations reveal a hypoglycaemia in a majority of cases, it is not surprising that Glucose has been advocated in treatment. The hypoglycaemia is possibly due to hepatic insufficiency; but it is indefinite as to how the glucose acts. It is most beneficial given on an empty stomach in doses of one ounce night and morning, in a little water suitably flavoured. The response to glucose depends upon the age of the patient. It is of greatest value in early life. The paroxysms definitely become less frequent. Nutrition and nervous control are greatly improved. It seems probable that glucose improves the general health and increases the ability of the organism to deal with foreign proteins which may enter the circulation. The liver undoubtedly plays a large part in the antigen-antibody reaction, and it functions best when liberally supplied with glucose.

Desensitisation with Proteose from the urine.

The method of preparing the proteose for skin testing and for desensitisation has already been described.

From the 1/1,000 stock solution, further dilutions of 1/10,000, 1/100,000 and 1/1,000,000 are made. Skin tests are then made by scratching

the patient's arm through a drop of each strength. A positive reaction is indicated by a more raised wheal with the 1/1,000 dilution than with the 1/1,000,000, the other two being intermediate. An intradermal injection is then made with the dilution which gives no response with the skin test.

For desensitisation, a dilution below that which gives a positive intradermal skin reaction is injected in gradually increasing quantities, at intervals of five to seven days. If an overdose is given, the patient has a severe attack of asthma, usually within a few hours. Some patients may complain of gastro-intestinal symptoms, such as vomiting and diarrhoea.

The theory of this form of treatment has much to commend it. It is as yet, however, too soon to decide upon its merits.

Liver Therapy.

Reference has previously been made to Mainwaring's demonstration that the liver is the site of the anaphylactic reaction in dogs. This and other material in previous sections lend support to the view that in asthma the action of the liver is defective. Therefore the employment of liver therapeutically would seem to be rational in this disease. Recent observations by Still(139) have

brought this subject to the fore.

In discussing the mode of action of liver, it is necessary to consider the state of the blood count. Many cases of asthma show a definite polycythaemia of over six million red blood corpuscles. This polycythaemia is not constantly present. Indeed the total red corpuscle count may vary in such patients from time to time by two and half millions. High red cell counts are usually found immediately following an attack and for varying periods up to one month afterwards. In the same patient, in periods of freedom from attacks, the count may be normal. This polycythaemia is most frequently found in patients in whom there is manifest allergy or in whom there is a well-marked family history of allergy. Moreover it is most frequently found in patients under forty years of age. As a rule, there are no accompanying symptoms. Nor does the presence of emphysema materially affect the count in the type of case under discussion. For the polycythaemia may be observed both in recent and in long-standing cases of asthma.

These observations would seem to indicate that polycythaemia in asthma has a definite relation to the state of the patient. A fall in the red cell

count may even be regarded as a sign of improvement.

It is said that the red blood corpuscles in the course of peptone shock are subjected to a dimunition of volume corresponding to the loss of fluid from the transudation of plasma through the dilated capillaries. This would appear to be the most likely explanation of this polycythaemia of asthma. The volume of the individual cell is decreased, and so there is an increased number of cells for each cubic millimetre of blood without an increase in the total cell volume or blood volume. That is, this polycythaemia is a relative one.

In those patients who respond favourably to liver therapy, investigation will reveal an initial high red cell count. Moreover, they will be found to belong to the definitely and clear-cut allergic type of asthma. The clinical improvement observed with liver therapy is accompanied in such patients by a fall in the red cell count. As such a fall does occur without the use of liver, it cannot obviously be attributed to it. Lowering of blood pressure, diuresis and lowering of the blood sugar - effects said to be produced by liver therapy - do not offer any satisfactory explanation as to how they may influence asthma. It seems probable that liver therapy may provide a substance which plays a part in the antigen-antibody reaction in

man, and which is lacking in patients suffering from asthma.

The liver is given daily over a minimum period of three months. Lightly cooked whole liver is but rarely tolerated for any length of time. A most convenient and efficacious preparation is one manufactured by British Drug Houses under the name of "Livogen". One ounce of this contains the active principles of four ounces of fresh liver combined with five grains of haemoglobin and the Vitamin B equivalent of one ounce of fresh yeast. It is given in doses of two teaspoonfuls once or twice daily.

The clinical improvement which follows liver therapy in suitable cases is pronounced. An outstanding feature observed is the change in the patient's expectation of the dreaded night. Sleep is greatly improved. Indeed, one patient under the care of the author, to whom three hours sleep had been for months a maximum, now regularly sleeps eight to ten hours and, on one occasion, twelve. The general physical and mental condition automatically improve. Life is no longer a mere existence, and interest is awakened afresh. It seems difficult for these patients to actually describe the change. They merely wish to continue the treatment.

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ACCOUNT OF CASES.

Sensitiveness may manifest itself in such a variety of ways that the kind of history-taking necessary in such a disease as asthma should be quite different from the clinical history required in other diseases. The description of symptoms is of infinitely less importance than the description of the circumstances under which they occur. It is essential that a thorough history and routine examination be completed. Special enquiries will enable us to elicit many points that are of great importance in the elucidation and diagnosis of allergic conditions. In an early case of asthma the only means of diagnosing the complaint is from the patient's history.

Each of the cases described hereafter has been summarised under the following list of headings, which were found of considerable value and convenience.

History.

Onset (date, month & year).
Course (with dates)
Attack related to:-
Season.
Place (changes in residence)
Domestic.
Occupation.
Diet.
Other changes.

Other Allergy.

In the past
At the present.

General health (by systems).

Headaches.
Sore throat and colds.
Appetite, indigestion and bowels.

The Attack.

Duration.
Frequency.
Relieved by:-
Coryza.
Wheeze.
Cough.
Sputum (amount and character).
Chest pains.
Other symptoms

Between Attacks.

Dyspnoea.
Cough.
Other symptoms.

General health (by systems) continued.

Micturition (Nocturia, frequency).
Menstruation.
Rheumatism.
Skin Lesions.
Weight (figures & dates).

Other diseases.

Past.
Present.

Family history of Allergy.

Antecedents.
Contemporaries.
Children.

Previous treatment.

Operations on nose and throat.
Specific and non-specific injections.
Drugs.

The date of onset is always important. Hypersensitiveness occurs with greater frequency in childhood. An early onset is suggestive. A close analysis of the season may suggest a particular protein. The character of the onset is also important, particularly its speed. A slow onset suggests a slowly developing infection; a sudden onset suggests a heavy exposure to some foreign protein or dust. It must, however, be remembered that the time relation between the exposure and the onset of symptoms varies widely.

It is important to understand the course of the symptoms. It should be noted whether this consists of definite attacks or whether it is relatively constant from week to week, month to month, and so on. A persistence of symptoms usually indicates an intrinsic cause of trouble, which the patient carries around with him. Isolated attacks do not always indicate a new contact with some foreign substance; for a large group of patients have asthma only with the "colds" which occur in Spring and the fall of the year.

The relation to changes in season and in residence are always of primary interest. Generally speaking, symptoms in Summer indicate pollens; and symptoms in Winter indicate infections, be they primary or secondary.

Changes in residence should be noted. The features to be considered include not only changes in temperature, humidity, altitude and vegetation, but also the social environment - whether the change was to or from the city, the suburbs or a farm in the country, and whether there was contact with animals in the old place, in the new, or both. If the move is not accompanied by any change in the symptoms, it is necessary to remember that

bedding, furniture, clothing and household pets may have been taken along and appear in the new place as well as in the old.

If the patient is relieved when he goes away from home, domestic dusts, as from feather pillows, toilet powders, soaps, articles used in the kitchen, like pepper - may be the cause of his allergy. Moreover, household pets are always potential causes of trouble to allergic individuals

Occupation should always be considered in its relation to symptoms. Freedom from attacks during vacations or when not at work should particularly be noted. The observation of such a feature may lead to the root of the trouble.

Diet must necessarily be investigated. Asthma has been identified with acute food poisoning. It is possible that specific hypersensitiveness may be present without the presence at the same time of corresponding skin reactions. Any changes in diet, which the patient may have made, should be noted. It is wise to enquire into the effects of starvation as treatment. In children, dislikes of certain foods are often of a protective nature. Later in life, overeating of a favourite food may equally be a cause of an attack. Should a specific food be

incriminated, it is interesting to observe whether symptoms are induced when the food is taken in its natural or raw state as compared with its treated or cooked state.

Many allergic conditions follow immediately on fears and emotions, whilst anticipation has a pernicious effect. In children, asthma may follow a party, the associated excitement being incriminated.

Intercurrent infections and any operations may be important. During any fever, all manifestations of allergy are prone to subside. Regardless of the nature, an operation is usually accompanied by a relief from the symptoms. Such a sequence may depend upon the sojourn in the clean hospital ward.

So it is clear that not only actual symptoms but every circumstance which might involve their appearance and disappearance must be considered. Indeed it may be truly said the history must be taken from the point of view of a detective rather than that of a doctor.

To obviate the possibility of missing important details in the investigation of the home conditions, the following table has been employed.

External particulars of the Home:-

(a) type of soil;

(b) locality - open or closed in;

(c) high or low ground;

(d) thoroughfare - busy or quiet;

(d) on bus route;

(f) garden or not;

(g) proximity to stables, factories, works;

(h) atmosphere - smoke, odours;

(i) other points of interest;

(j) other known cases of asthma in locality;

Internal particulars of home:-

(a) duration of patient's residence;

(b) damp or dry;

(c) type of heating - coal, gas, oil electric;

(d) floor of house used;

(e) number of rooms used;

(f) whether crowded with furniture;

(g) presence of plants indoors;

(h) whether well lighted;

(i) adequate window space;

(j) ventilation particulars;

(k) whether windows open day and night;

(l) freedom from dust;

(m) cleaning methods;

(n) carpets, linoleum, rugs used;

(o) walls - whether papered, distempered, painted;

(p) (1) cushions.)
bedding.) whether of horsehair,
pillows.) feathers, flock, kapok;
upholstery)
(2) whether feather eiderdown used.

(q) pets kept - cats, dogs, chicks, rabbits, mice, guinea-pigs, birds;

(r) other points of interest.

The History of the Attack may include certain features which throw some light upon its cause. A sudden onset suggests a true extrinsic fact; a slow and gradual onset points to a slowly developing infection. A slow onset may however, also be due to a low degree of sensitiveness which is not manifest unless the exposure is heavy.

Symptoms in general are concerned mostly with the wheeze and cough. Fatigue, debility and loss of energy are not common; but such general symptoms may appear when the severity of the attack has reached a certain point. The dyspnoea is obstructive in type and paroxysmal in nature; but in advanced cases it tends to be continuous. Breathing is audible and usually conscious. Ordinarily expiration is more distressing to the patient than inspiration. It is long drawn out and accompanied by the characteristic wheeze. The respiratory difficulties are usually most intense at night; this fact serves to differentiate a true asthmatic dyspnoea from cardiac dyspnoea; for the sufferer with the latter usually sleeps well.

Coryza is an important symptom at the onset. It may be preceded by itching of the eyes, soft palate or throat, and sneezing. There may be

copious watery nasal discharge and nasal obstruction. Local symptoms such as these may, however, not be observed. It is important to realise that their absence in no way excludes an extrinsic factor.

Cough is rarely present at the onset of an attack, but is a frequent accompaniment of its termination. When marked, it indicates an enlargement of the bronchial glands withchronic irritation of the bronchi therefrom, and a chronic irritation of the bronchial walls themselves, either a peribronchial fibrosis or a bronchitis. Sometimes cough does not occur until adrenalin is administered.

The sputum varies in accordance with the amount of secondary infection. Frequently there is a history of the raising of a quantity of this sputum following the relief of the bronchospasm by adrenalin. Once the asthmatic patient develops a secondary infection the sputum increases in amount and consistency. Three components of the sputum of asthmatic patients have received much attention. The first was described in 1872 by Leyden as the cause of asthma, and consists of colourless hexagonal crystals, called Charcot-Leyden crystals. They are rarely seen nowadays, and are now thought to be due to chemical decomposition. The second component described is the Laennec "Perle", which appears as a ball of tough opaque material like

tapioca and of about the same size as this. Some are mere mucous moulds of the smaller tubes, whilst others are ravelled Curschmann's spirals, the third element to be described. The latter were first described by Curschmann in 1882. They are composed of strands of fibres wound round a central, white, homogeneous filament, and contain in their meshes eosinophils, leucocytes and epithelial cells. They occur particularly at the end of a paroxysm, and are absent usually if the sputum is mucopurulent.

The bacteriology of the sputum has been very thoroughly investigated. All kinds of organisms have been described. The significance of the organisms is difficult to determine. It must not be forgotten that normal, non-asthmatic, apparently healthy individuals may harbour a great variety of organisms in their throats. Furthermore, such germs as the haemolytic streptococci, which are ordinarily considered more virulent than others, may be found to be present in the throats of practically all normal adults. Such findings are to be explained by the new knowledge of the great distinction which exists between virulent and avirulent strains of organisms, which otherwise appear to be very similar. At least, the growth on ordinary media is similar. The relation of the sputum bacteria

to asthma has not been determined altogether. It has been shown that if pure cultures of a number of bacteria are used for vaccines or for bacterial proteins, and if skin tests are made with these products, certain organisms in the number will cause skin reactions. Such reactions are not, however, of the immediate variety but delayed, occurring in twenty-four hours as red swollen areas of inflammation. When in this way different organisms are tested on different individual patients, in most of the cases tests will differ enough among the patients to demonstrate a certain specificity of the different organisms. On the other hand certain organisms, especially of the Gram-negative variety, react in a considerable proportion if not in all of the patients tested. Therefore it seems unwise at present to rely much on skin tests to bacteria or their products as reliable diagnostic aids. Knott, working at the Guy's Hospital Clinic, has taken this investigation a step further; he points out the importance of determining the actual bacteriology of the spirals as against that of the sputum as a whole; for he lays stress on the finding of Gram-negative bacilli of the B. Friedlander group in the

spirals. Many of these bacilli are histamine producers, and it is interesting to note that a spasm-producing substance has been found in the sputum during asthmatic attacks, which was absent during the free intervals and in other diseases. Abdominal and Gastro-Intestinal Symptoms are rare. Vomiting is infrequent, except in childhood, when of course, it is apt to be followed by relief and consequently encouraged. The appetite remains good. Patients know however that food in the stomach is apt to induce dyspnoea. Loss of weight indicates not so much the severity of the dyspnoea as its persistence. Indigestion is unusual on a whole. Constipation is not usually a symptom.

Bladder symptoms are rare and appear to have little to do with asthma.

Menstruation is similarly not affected, except in so far as an attack may render a period present at the time worse.

Rheumatism and pain in the extremities is uncommon.

The Past History of other diseases is sometimes of value. It is wise to determine this from infancy, if possible. It is not al all uncommon to learn that the period of weaning was a difficult one, owing to gastric and intestinal upsets.

Eczema may have appeared on the face at a few months of age and have persisted during infancy, after which it may have cleared from the face and appeared at the flexures. Later in life attacks of urticaria may have caused much inconvenience. Quite one of the commonest histories is that the patient was subject to frequent attacks of bronchitis, or has had several attacks of pneumonia.

Naso-pharyngeal affections are frequent, and in chronic sufferers it is rare to find one in whom nasal operations have not been undertaken or suggested.

Moreover, it may be found that the original onset of asthma occurred after some acute infection like pneumonia or even appendicitis, in which the resistance of the patient is lowered in some way so that a hypersensitiveness may develop.

It must be remembered that asthma usually disappears during fever and immediately after surgical operations. The various circumstances of rest and change in environment may undoubtedly play their parts.

The Family History is always important. Inheritance is one of the principal criteria of allergy. Moreover, the incidence of a positive family history is more frequent in the extrinsic

group than in the intrinsic. It is necessary to pay particular attention to a history of allergy in general and not particularly to a single manifestation. Inquiry should be made for a history of asthma, hay-fever, eczema, urticaria, pruritus, migraine and perhaps for digestive derangements, in relatives or children. It is said that the greater the number of affected relatives the earlier will the patient have had the onset of symptoms, the greater the number of allergic manifestations that will be shown and the greater the number of substances to which there will be a hypersensitivity. Any information relating to the prevalence of renal or cardiac disease or tuberculosis of the lungs, should be followed up, as it is frequent for symptoms of these affections to be mistaken for asthma. And another useful hint is a history of "nerves" in a family.

The History of Previous Treatment is of great value in planning future treatment. It should not be neglected . If the sinuses have already been drained, caution should be exercised in advising a repetition of this procedure. Courses of treatment with extracts or vaccines, and their results, will indicate the wisdom of advising them again.

The same may be said about drugs. Deliberate changes in environment and any journeys or vacations should be noted with respect to any improvement or aggravation of the asthma during the change.

Physical Examination.

Undoubtedly this is of foremost importance. An attempt should be made to describe the gross appearance. Attention to uniformity as much as is possible should be aimed at. Asthma occurs about equally in men and women, and both in those who are tall and thin and in those who are short and fat. Blondes and brunettes are about equally affected. All different races may be seen at various times.

The colour is usually normal. Cyanosis is due to a faulty oxygenation of the blood caused in turn by a secondary bronchitis, or more often by a thickening of the larger and smaller bronchi. Clubbed fingers should always be looked for.

The skin is ordinarily clean. In children especially, eczema may be an accompaniment; its presence points to an extrinsic cause to explain both conditions.

Scratching with the finger nail brings out, in normal people, either a white or a red line which depends respectively upon the contraction or

relaxation of the superficial capillaries. The white line was thought to denote an insufficiency of adrenalin in the blood; but so far this theory has not been proved. The red line is part of the normal response. The intensity of the response varies widely in both allergic and normal individuals.

The examination of the nose should be thorough and methodical. Many asthmatic patients have a definite nasal voice, which indicates acute or chronic disturbances of the paranasal sinuses - such a voice is usually found in the more advanced cases. It should be observed whether the mucous membrane is red and normal in thickness or pale and swollen and boggy. An appearance such as the latter on one side would perhaps indicate a chronic lesion in the nose or sinuses on that side. Transillumination may reveal definite trouble in some sinus.

Large tonsils, particularly if associated with a sore throat or with palpable glands in the neck, warrant great consideration. They may act as a focus of infection to aggravate the asthma, and their removal may do a great deal to improve the condition of the patient. Small tonsils, with ragged surface and blocked crypts, also deserve attention, particularly if the patient suffers from

repeated sore throats and has enlarged glands in the neck.

The naso-pharynx is normally smooth, pink and moist. Patients with asthma frequently show not only islands of lymphoid tissue on the pharyngeal wall but they may also show a marked dryness of the pharyngeal mucosa, often with dry sticky material adherent to it. These same persons may have a mass of thick mucus about to descend from behind the soft palate. All these abnormal conditions suggest the presence of infection in the sinuses above.

The teeth should be examined with great care. The removal of a tooth, with an abscess at its root, has occasionally resulted in very marked improvement in an asthmatic patient. It is wise to be suspicious of all gold crowns, bridges and large fillings. In addition, it is easy to see whether the teeth, in upper and lower jaw, articulate sufficiently well for proper mastication.

The Outline of the Chest is to be carefully observed. Severe and persistent asthma may occur without chest deformity. The end results of long standing bronchitis, asthma and emphysema, however, are a bent forward posture and barrel-shaped chest.

The Heart may often appear small in size clinically, whereas X-rays may show it to be normal.

This may be accounted for by the associated emphysema, which renders the peripheral lung lobules larger so that they come to lie between the pericardium and the chest wall, thus interfering with the percussion of the cardiac borders. The emphysema may also interfere with the heart sounds, causing them to be diminished in intensity. In many cases, the heart is central in position and of the long, low type.

The blood pressure is low, especially during the attack. A characteristic feature of patients with asthma is the difficulty of obtaining blood pressure readings during inspiration. The discrepancy in the systolic pressure taken during inspiration and expiration may be wide. This respiratory variation in blood pressure is roughly parallel with the severity of the asthma. It is of course only observed during the paroxysm, when the patient is suffering from dyspnoea. The phenomenon is probably due to the fall of intrathoracic pressure which occurs during inspiration, sucking the blood back from the vessels into the chest.

The physical signs in the lungs depend upon various factors, such as the presence or otherwise of an acute attack, the length of time the patient

has been a sufferer from asthma, and the presence of complications. While a patient may consider himself well, it is not uncommon to find some hyper-resonance and a high pitched quality of expiration which indicates the persistence of more or less stretching of the lungs - emphysema. There may be no rales in such a case. In an acute attack rales of all kinds are to be heard, and may even be felt; expiration is prolonged; and the lungs are hyper-resonant. The rapidly shifting physical signs of asthma obviously depend upon the filling with secretion and subsequent clearing of the bronchi.

The abdomen shows nothing characteristic in asthma. Flaccidity and distension may occur during the attack or between attacks. Such distension may prove embarrassing to a patient; and if it is relieved by an enema, a paroxysm of asthma may be considerably shortened. The liver may be pushed down by the distended lung.

The genitalia are usually normal. As a system it should however be carefully examined.

The extremities show no change beyond emaciation in the more advanced cases. Clubbing of the fingers and toes may be found, especially in those

with barrel shaped chests and long-standing asthma.

The urine is normal in asthma. It, like the blood and sputum, should be investigated both during the spasm and in the interparoxysmal period.

In the blood, the one constant characteristic to be noted is the presence of an eosinophilia, the percentage of which may reach fifteen.

The objects of a thorough physical examination are:-

1. To discover the presence or absence of damage to the lungs;
2. To detect signs of cardiac or renal dysfunction;
3. To investigate any focal sepsis;

With these objects in view, laboratory tests and X-rays are found most helpful. Protein skin reactions may indicate a causal factor. The tuberculin skin reaction and the Wassermann reaction have each their place in the necessary investigation.

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CASE NO. 1.

Name:- Phyllis Cox.

Age:- 30 years.

Occupation:- Housemaid

Address:- Thicket Grange, Sandis-platt Road, Maidenhead.

Single.

Date of Examination:- January 11th, 1930.

Complaint:- Attacks of dyspnoea, of sudden onset, occurring in the early hours of the morning, associated with wheezing and cough.

Duration of Illness:- 7½ years.

Onset:- March 3rd, 1925

History. Personal.

On July 21st 1920, she developed a cough of a dry, rasping nature. She was then working at Newbury, Berkshire. The cough persisted but changed in character and became loose. As it continued in spite of home treatment, she consulted her doctor in January 1921. Consequent on this consultation, she was seen by the Tuberculosis Officer and sent to Peppard Sanatorium. She was discharged in January 1922, her weight being then 7 stone 5 lbs. In May 1922, she had a return of the cough, but it did not last long. In 1924 she

came to Maidenhead. In November of that year the cough again returned. Her weight was then 7 stone 7 lbs. No signs of active tuberculosis were found clinically and her sputum did not contain tubercle bacilli. The cough left in about four weeks.

In March 1925, she was working in Hayes, in Middlesex. There she had an attack, which was diagnosed as asthma. It began like an ordinary "cold" and then spread to her respiratory system. So that the asthma was gradual in onset and occurred at the age of 23.

Since this date, the patient has had twelve definite attacks of asthma, which have occurred in spring and early summer. They usually begin at 3 a.m. and persist for about 24 hours.

(a) Factors influencing an attack.

A high temperature and a foggy atmosphere appear to predispose to an attack. The dust from carpets and feather pillows make her wheezy. Similarly, in the presence of horses, she is uncomfortable about her nose and chest. Certain articles of diet - bananas and tomatoes when eaten raw, and eggs - give her indigestion, which is apt to precipitate an attack; cooked bananas and tomatoes do not affect her. She has also noticed a tendency for chest symptoms to appear when she becomes excited or nervous.

Changes in residence do not influence the asthma of this patient. She has never worked or lived in a city or town. At the same time, she has never had an attack during a vacation, and has noticed that she felt particularly well at Brighton.

(b) The nature of the attack.

The attack is preceded by certain prodromata. These are:-

Itching of the soft, palate, upper lip and auditory meatus.

It is relieved by sitting up and trying to keep quiet. Should vomiting occur, the patient immediately feels much better.

Coryza is a well marked symptom, the nasal discharge being free and the nasal passages becoming as though obstructed.

Wheezing does not appear unless the attack is very severe.

A cough usually follows the wheezing. It is paroxysmal in nature and is relieved by expectoration.

The sputum is small in amount, and muco-purulent in character.

When wheezing is present, it is accompanied by mid-sternal pains of a dull aching character.

The patient complains also of certain symptoms. First is constipation, which is said to become

worse just prior to an attack. During the attack she also has a frontal headache. Pain in the interscapular region and in the right hypochondrium has been experienced at times during attacks.

(c) Health between attacks.

She is subject to premenstrual headaches which are relieved by the onset of the menses.

She suffers from constipation for which she is always taking aperients. Her appetite is small.

She is subject to rheumatic pains of indefinite nature in damp weather.

(d) Other diseases.

Past. Measles) As a child; there were no
Varicella) complications.

There is no history of eczema in infancy nor of repeated attacks of bronchitis.

Present. None.

(e) Other allergy.

Past. She was subject to "bilious attacks" up to the age of puberty, when they ceased.

At twelve years of age, she had a severe attack, of urticaria, the cause of which was undiscovered.

In June 1930, she had an attack of hay-fever.

In July 1930, she had an attack of migraine.

Present. At odd times she is liable to itching and congestion of the conjunctivae.

History. Family.

Both her father and mother are alive. The former suffers from arthritis and the latter from migraine. She has three sisters, all of whom are alive and well. One suffers from nephroptosis, following childbirth.

History of Previous Treatment. (Asthma.)

As the attacks have usually been associated with a slight temperature, she has been confined to bed during them and kept on a fluid or semi solid diet.

Treatment has hitherto mainly consisted of the use of inhalant powders - Potter's in particular - and anti-spasmodic drugs, such as Lobelia. The former appeared to prolong her cough, and the latter make her feel ill.

External Particulars of Home.

In her present situation she is living on a clay soil, on low ground; there are large houses around, with big gardens in between. The main Great West Road, a very busy thoroughfare, is about a hundred yards away. The atmosphere is clear and fresh, there being no factories, etc. nearer than four miles. She sleeps in a room facing north.

There are no other known cases of asthma in the locality.

Internal Particulars of Home.

She has been 2¼ years in her present residence. The house is dry. It is central heated, but coal and electric fires are also used at times. The floor is wood on cement.

Ten rooms are used; they are not crowded with furniture.

No plants are kept in the rooms.

The house is well lighted, but the window space is inadequate.

Ventilation is good. The windows are kept open night and day.

The house is not dusty. The house is cleared by dusting and polishing with Mansion polish.

Five rooms have linoleum; the others have carpets. There are four hair rugs.

The walls are all distempered.

	Horsehair.	Feathers	Flock	Kapok
Cushions	+ +	+ +	+ +	0
Bedding	+ + +	+	0	0
Pillows	0	+ + +	0	+
Upholstery	+ +	+	0	0

Feather eiderdowns are used.

In patient's own room were hair cushions,

bolster and mattress, with feather pillows and eiderdown.

Two dogs are kept in the house.

State on Examination.

She was of average intelligence.

Height - 5 ft.

Weight - 7 stone 7 lbs.

Development normal, but rather thin.

General appearance sallow and dark under the eyes.

No cyanosis present.

Temperature normal

Respiratory System.

Subjective phenomena.

The cough has been described. It is only present during an attack; and it is always of the same nature.

Dyspnoea is not present, except during an attack, when it is definitely obstructive in type and paroxysmal. The extraordinary muscles of respiration are then brought into play.

Pain is absent also, except during an attack when it is experienced down the middle of the sternum.

There has been no haemoptysis.

Respirations are 18 per minute. Breathing is costal or thoracic in type. The rhythm is regular.

Sputum. This is scanty, and greyish in

colour. It is frothy and mucopurulent in appearance. Microscopically, it is seen to consist of many types of cocci, eosinophil cells, Charcot Leyden Crystals and Curschmann's spirals. The cocci on cultivation prove to be pneumococci and streptococci viridans.

Naso-Pharynx and Larynx.

The nose is straight. The alae nasi do not bulge on inspiration. There is no nasal interference with respiration and no nasal discharge. The septum is neither deflected nor perforated. The turbinates are not enlarged but appear normal. There are no polypi to be seen. Posterior rhinoscopy does not reveal any abnormality. Transillumination fails to show disease of the sinuses; nor is there any tenderness over the frontal or maxillary sinuses.

The tonsils are normal in appearance. The colour of the anterior pillars of the fauces is brighter than normal, and contrasts with the normal colour of the uvula and soft palate. The pharynx has on its surface a number of flat adenoid swellings like sago grains. There is no excessive mucus present. The larynx is normal. The voice is soft. Words are run into each other, which makes pronunciation of words indistinct.

Thorax. The chest is of the flat type.

Measurements:-

Anteroposterior diameter - 6½ inches.

Transverse diameter - 8 inches.

Circumference - 30 inches.

Thoracic Index $\left(\frac{\text{anteroposterior diameter X 100}}{\text{transverse diameter}}\right)$ = 81.25

Expansion - 2 inches

Subcostal angle - 80 inches

The movements of the chest are normal.

1. Breathing being costal in type;
2. The chest expanding equally and uniformly;
3. Respiration being 18 per minute;
4. Inspiration being separated from expiration by a definite pause.

Litten's diaphragmatic sign was not observed.

Palpation.

The chest is flattened anteriorly. No glands are palpable. Movements are equal on the two sides and uniform. Vocal fremitus is absent, except over the sternum.

Percussion.

Anteriorly.

Krönig's isthmus measures at its narrowest point:-

Right side - 2 inches.

Left side - 1¾ inches.

In the infraclavicular regions, the percussion note is louder on the left side, as is normal.

Nowhere is hyper resonance nor dullness observed.

The sense of resistance to percussion is not increased.

Tidal percussion shows a restriction of the extent to which the lung descends on inspiration on the left side; indeed, it descends ¼ inch lower on the right side, thus reversing the usual findings.

Auscultation.

The breathing was broncho-vesicular in type. This is particularly well marked in the left infraclavicular region.

No accompaniments were detected.

Vocal resonance is diminished throughout.

D'Espine's sign was negative.

X-ray Examination.

This showed no evidence of tubercular infiltration. Throughout both lungs a moderate degree of peribronchial shadows is noticeable. The posterior mediastinum is clear. The diaphragm is lower on the right side.

Clinical Condition During an Attack of Asthma.

The patient was cyanosed and sweating, with

cold extremities and a feeble pulse.

Dyspnoea was present.

The chest was full and fixed, remaining largely in the inspiratory phase.

The diaphragm was low.

The pleuro-costal sinus was obliterated.

The costal margins during inspiration moved toward the middle line.

Respiration was much restricted and almost entirely costal.

The chest expanded very little, in spite of the activity of the extraordinary muscles of expiration. Sigson's furrow was well marked.

Percussion showed generalised hyper-resonance, of lower pitch than normal.

On auscultation, a loud wheezing was audible during both phases of respiration.

Inspiration was feeble, rapid, short and comparatively noiseless; expiration was abnormally loud, much prolonged, and very moist.

Sibilant and sonorous rales were well defined.

The cough was very tight and violent, with the expectoration of clumps of tenacious mucus.

Haemopoietic System.

No subjective phenomena.

A few small and discrete lymphatic glands palpable in posterior triangles of the neck.

Ductless glands - no abnormality.

Blood.

Size of red corpuscle	7 μ
Haemoglobin	75%
Red Corpuscles.	4,340,000
White corpuscles.	10,240.
Colour Index.	.87

Differential Count.

Polymorpho-nuclears	50.3%
Small lymphocytes	30.3%
Large mononuclears	12.6%
Eosinophils	6.5%
Basophils	0.3%

Arneth Count.

No. 1 type	0.4%
2 type	10.0%
3 type	38.4%
4 type	37.2%
5 type	14.0%

Wassermann - negative

Van den Bergh reaction - indirect.

Blood bilirubin - 0.3 mgm per 100 c.c. plasma.

Blood calcium - 10 mgm per 100 c.c. "

Blood sugar - 60 mgm per 100 c.c. "

Circulatory System.

The dyspnoea and cough present in this patient could not be attributed to any disease of this system.

Pulse. Arterial wall not palpable.

Frequency - 78

Rhythm regular, except for presence of sinus arythymia.

Blood pressure - systolic 130

diastolic 74

Heart. No pulsations visible on inspection, except in the epigastrium towards the end of expiration.

Apex-beat just palpable in the sixth interspace $2\frac{1}{2}$ inches from mid-sternum.

Borders - $\frac{\overline{111}}{\frac{1}{2}/2\frac{1}{2}}$

There are no murmurs.

X-rays show a long and narrow heart shadow, no bulging and a clear posterior cardiac space.

Urinary System.

No subjective phenomena.

Urine. Lemon-coloured and clear.

43 oz. in 24 hours; proportion of day urine to night urine 3.3 : 1

Specific gravity 1,006.

Acid reaction, Ph 6.7

Urea excretion on a standard diet - 2%

No abnormal constituents.

Deposit - nil to observe.

Paroxysmal Urine.

Reaction acid.

Specific gravity 1,020.

Ether reaction well marked.

Urine clears on heating, showing presence of urates.

Urine smells strongly of ammonia.

Excretion of chlorides is lower than normal, as determined by the nitric acid and silver nitrate test, when only a milky solution is obtained.

Alimentary System.

No subjective phenomena, except occasional flatulence.

Teeth - good.

Bowels - constipated.

Faeces - darkened in colour - formed and hard - neutral reaction - Benzidin test for occult blood negative - no tubercle bacilli present - no abnormal ingredient.

Abdomen - Abdominal walls flabby. Colon palpable in the left inguinal fossa, containing faecal material.

Test Meal.

Total acidity - 45.

Free Hcl. - 0.06 per cent.

Laevulose tolerance test.

Blood sugar does not rise above 0.12 per cent, and the curve is normal.

Integumentary System.

Reaction of skin to stroking - positive.

Skin tests:- Hair - + (dog + +)

Feather - +

Delayed skin test to streptococci and pneumococci +

Von Pirquet's tuberculin test - negative.

Reproductive System.

Catamenia began at 13 years; lasts four days; 4 weekly; clotty.

Nervous System.

Higher cerebral and mental functions normal.

Cranial nerves normal.

Cervical sympathetic normal.

Motor functions normal.

Reflexes normal.

Sensory functions normal.

Vasomotor and Trophic functions normal.

Locomotory system normal.

Diagnosis.

Asthma:-

Type 1 - Adults.

Subtype (a).

Treatment.

The Attack.

(The following procedure proved most efficacious)
Liquor adrenalin hydrochloride 0.25 c.c. subcutaneously.
Room warmed but well-ventilated; quiet and restful.
A small cup of strong black coffee given.
Back rubbed with unguent capsicum.
Hot-water bottles applied to feet.
A soap and water enema administered.

Diet.

Fluids only till free from symptoms. Four to five pints in 24 hours - whey, albumen water, chicken essences, Glaxo, soda water - in small quantities every two hours.

One week following attack.

Ephedrine hydrochloride gr. ½ at bedtime.
Potassium iodide gr. 10 twice daily, or Eupnine (caffeine iodide) 3ŧ morning and evening.
Magnesium sulphate 3 ss each morning.

Blood therapy:-

4 c.c. withdrawn from the arm and immediately injected into the buttock twice during the week at equal intervals.

Diet.

No eggs, bananas, tomatoes allowed.
Glucose - 3ŧ - morning and evening - in a

little water on an empty stomach.

The Fundamental Cause.

She was advised to resign from her post, and she very conveniently got married. The opportunity was therefore taken to institute a vigorous routine.

The home to which she went was on high but sheltered ground in a locality not subjected to fogs and mists.

No feather cushions nor eiderdowns and no hair cushions, rugs nor mattresses were allowed. Parquet and linoleum composed the floors, there being no carpets.

No dogs or cats were allowed to be kept, and she was advised not to go near cows nor horses.

Eggs, bananas and tomatoes were to be eaten but sparingly. Double the usual amount of sugar eaten was to be taken, and sweets encouraged.

Liver, in the form of "Livogen", was given twice a year for periods of three months at a time in doses of 3 ŧ morning and evening.

She had a course of abdominal massage and exercise for her constipation, and was advised to avoid going twenty-four hours without a motion.

Her throat was sprayed every morning and evening with Dobell's Solution, and painted once a week with Mandl's pigment (half strength).

Salicylates were advised for her rheumatism.

From 27.1.30 to 14.4.30, a course of an autogenous vaccine, composed of the streptococci and pneumococci from her sputum, was administered. The doses ranged from 5 to 200 millions at weekly intervals.

She has monthly doses of a prophylactic vaccine - anticoryza No. 4 of Burroughs, Wellcome & Co. - from September to April.

A mixture of the proteins from animal's hairs and feathers, to which skin tests were positive, was administered. The stock solution was diluted 1 in 10, 1 in 100, 1 in 1,000, 1 in 10,000 and 1 in 100,000. Using 1/20 c.c. intradermally and considering as a positive skin test a wheal of one inch in diameter, 1 in 10,000 was the weakest solution to which she reacted. Treatment was begun with 0.1 c.c. of this strength of solution. The dose was doubled each time at weekly intervals. Treatment occupied nearly five months. Skin tests were negative to the stock solution on completion of the course.

Progress Notes.

June 1930 - Hay-fever.

For prophylaxis against this, she received injections of pollen from the following grasses-

Timothy grass, Rye grass and Meadow grass,

to which she reacted positively, in the Springs of 1931 and 1932. This has been successful in avoiding further hay-fever attacks.

July 1931 - Migraine.

February 1932 - Acute infectious catarrh.

State on examination - October 1932.

No further attack of asthma since completing treatment.

Weight has remained steady at 7 stone 12 lbs. and general health excellent.

Blood count now normal, except for the eosinophilia.

No constipation now present.

Skin tests to hair and feathers now negative; and diet not now restricted.

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CASE NO. 2.

Name:- Elsie Leader.

Age:- 26 years.

Occupation:- Shop Assistant.

Address:- 32 College Glen.

Single.

Date of Examination:- December 17th 1929.

Complaint:- Sudden attacks of dyspnoea occurring in the early hours of the morning, associated with a tightness in the chest, and followed by a cough.

Duration of illness:- 5½ years.

History. Personal.

In March 1926, she had an attack of influenza of the respiratory type. It consisted of a sudden attack of fever, general pains and a dry, hard cough. The fever and pains lasted about ten days; but the cough, having changed in character and become loose, persisted. She consulted her doctor about the persistent cough. She was seen by the Tuberculosis Medical Officer and sent to Peppard Sanatorium. No tubercle bacilli were found in her sputum. She remained at Peppard for six months and had no cough on discharge. In

November 1926, she developed an acute infectious catarrh. Two nights after the onset of this, she awakened at 3 a.m. with sudden dyspnoea, wheezing sounds in her chest and a violent paroxysmal cough. This was her first real attack of asthma. Since then she has had innumerable attacks. At first they occurred during the Winter and Spring. Now she is hardly every free from the cough and tightness in her chest.

(a) Factors Influencing an attack.

Strong winds are very liable to bring on an attack. At one time the attacks seemed to develop just prior to the onset of menstruation. Indigestion undoubtedly predisposes her to a paroxysm. Dusts of any kind lead to symptoms of wheezing and cough; for this reason she had to resign her post at a dry cleaning establishment. It is noteworthy that she remained free from symptoms when away from home at Peppard and Margate.

(b) The nature of the attack.

The attack is preceded by certain prodromata. These are:-

1. a dull aching pain and discomfort over an area corresponding to Traube's Semilunar space, extending from the left mid-axillary line to the left parasternal line and from the left fifth intercostal space above to the costal

margin below.

2. extreme irritability;

The attack may now last 24 hours. At first the attacks occurred about once a month during the Winter and Spring; now they are more frequent, and indeed she is never free really from the cough.

The attack is relieved by spraying the nose with adrenalin, and by taking ephedrine. At first, Potter's powder used to give relief, but not now.

There is no coryza.

Wheezing is well-marked and audible to those in attendance on her.

The cough is paroxysmal and comes on when the attack of wheezing is passing off. It is hard and relieved by the expectoration of tenacious sputum. In about twelve hours the cough is looser and greenish-gray sputum in small quantities is expectorated.

There are no pains in the chest.

The only other symptom complained of is frontal headache.

(c) Health between attacks.

The patient never really feels well. She suffers from fatigue, debility and loss of energy. Dyspnoea arises if she attempts to hurry or do any manual work. The cough is very troublesome.

She complains a lot of tightness in the chest. She feels as if an attack was impending all the time.

Her appetite is fairly good, and she does not suffer from constipation.

(d) Other Diseases.

Past. Measles at age of 4; no complications.
Influenza 1926.
Tonsillectomy 1922.

Present. Migraine.

(e) Other Allergy.

Past. Migraine.
Hay-fever.

Present. Migraine.

History. Family.

Father was killed in Great War.

Mother, two brothers and two sisters alive and well.

Allergy in family.

Antecedents. Paternal Grandmother - asthma.
Paternal Grandfather - "chest trouble"
Mother - Urticaria.

Contemporaries. One sister - eczema and hay-fever.
Another sister - asthma - (relieved by tonsillectomy)

History of Previous Treatment.

This seemed to have been chiefly symptomatic. It consisted of Lobelia and expectorants for the respiratory condition. Indigestion was treated with carminatives when it arose.

A change in environment, as to Peppard, freed her of attacks until her return home.

General Surroundings at Home.

She lives in a small semi-detached house in a short street, crowded with houses, but wide and airy. Her mother is neurotic and too sympathetic.

External particulars of home.

She is living on a gravel soil, on fairly high ground. Her home is in a well-populated district. The street is not a bus route but is not quiet. There is a small garden. There is no factory nor works within one mile. The atmosphere is clean, there being no smoke nor odours.

There are three other cases of asthma in the locality.

Internal Particulars of Home.

She has lived in her present home since birth. The house is dry. It is heated by coal fires. The floor is wood, on cement foundations.

Five rooms are used, which are crowded with furniture.

No plants are kept in the house.

The house is dark and not well lighted.

The window space is inadequate, and ventilation is poor; windows are kept open day and night.

The dust from the street is very troublesome. The house is cleaned by dusting.

The floors are covered with linoleum; there are some woollen rugs.

The walls are all papered.

	Horsehair.	Feathers.	Flock	Kapok.
Cushions.	0	+ +	+	0
Bedding.	+	+	-	+
Pillows.	0	+	+	0
Upholstery	+	0	0	0

Feather eiderdowns are used.

In patient's own room, there are no articles containing feathers.

No pets are kept.

State on Examination.

She is of average intelligence.

Height - 5 feet 7 inches.

Weight - 8 stone 2 lbs.

Development is normal.

In her general appearance, she is thin, with sharp features and square shoulders.

Her expression is that of a tired person, with darkened areas under the lower eyelids.

In her attitude, she is inclined to give way to her affliction.

Her complexion is sallow, with a suggestion of cyanosis.

Her temperature is normal.

Respiratory System.

Cough is very persistent. It is paroxysmal in nature, being hard and followed by the expectoration of tenacious sputum. It is worse in the early morning. Towards the end of the an attack of wheezing, it becomes exhausting in its persistence.

Dyspnoea is of two types. During an attack of asthma it is expiratory, with prolonged laboured expiration. In between attacks, it is inspiratory and appears on exertion. The expiratory type may suddenly begin about 3 a.m. and last until relieved probably about one hour. It is followed then by the troublesome cough.

Cyanosis is of the "pale" type, there being a generalised dusky leaden hue, indicating disturbed respiratory functions. During an asthmatic attack, it becomes "dark", indicating cardiac embarrassment. The lips, cheeks, nose and ears, over the hands and feet, and over the knees show it most conspicuously. The dark cyanosis occurs when the

when the chest remains in the inspiratory phase and is expanded very little by the vigorous respiratory efforts.

Haemoptysis has not occurred. There have been no chest pains.

"Tightness in the chest" in complained of at the time of an attack. In the so-called free intervals, she never seems able, she says, to get a free inspiration. In other words, respiration seems unsatisfactory.

Breathing. This is predominantly costal in type. The scaleni and upper intercostal muscles are used more than normal. The rhythm is regular, but somewhat jerky. There are 18 respirations per minute.

Sputum. This is scanty, but more profuse after an attack. It is purulent and greyish in colour. It is frothy and contains Charcot-Leyden crystals, Curschmann's spirals, eosinophils and innumerable cocci. The latter, on cultivation, prove to be streptococcus viridans, staphylococcus aureus and micrococcus catarrhalis. Tubercle bacilli are not present.

Naso-pharynx. The nose is straight and narrow. The right turbinate - inferior - is covered with swollen, boggy mucous membrane, which is encroaching on the nasal septum which is

straight. The pharynx is covered with granulations and very congested. There is a catarrhal discharge trickling down from the posterior nares.

The uvula and fauces are redder than normal.

The right antrum is opaque to transillumination.

Thorax.

Inspection. The chest is funnel-shaped. Its circumference is greatest midway between the clavicular and costal borders. The jugular and supra--clavicular fossae are very prominent. The shoulders are square.

Measurements.

Anteroposterior	8 inches.
Transverse	9 inches.
Circumference	30 inches.
Thoracic Index	88.8
Expansion	2 inches.
Subcostal angle	68°

Sigson's furrow is well marked.

Litten's diaphragmatic sign is not present.

The respiratory movements appear forcible, but are inefficient and laboured.

Inspiration and expiration appear equal in length. There is retraction of the upper abdomen on inspiration.

Palpation. This confirms the details of

form and movements determined on inspection. Vocal fremitus is decreased generally but not lost.

Percussion. The note is loud, full and drum-like. The pitch is lower than normal. This hyper-resonance varies over different parts of the chest, and is particularly marked in the left infraclavicular region. Tidal percussion is equal on the two sides and measures 1½ inches. In the interscapular region the percussion note is duller than normal and is of a higher pitch; and the sense of resistance to percussion is increased.

Auscultation. The breath sounds are faint and expiration is prolonged, the normal ratio of 3.3 to 1 being reversed. The inter-respiratory pause is lengthened. The breath sounds are wheezy and harsh and associated with coarse rales and sibilant rhonchi, which in places mask the breath sounds. Vocal resonance is diminished generally. In the interscapular region, the breath sounds are bronchial in type; and vocal resonance is increased.

D'Epine's sign, or the presence of whispered pectoriloquy over the spinous processes of the fourth and lower two thoracic vertebrae, is present.

X-Rays.

Show no evidence of tuberculous infiltration.

Lung shadows are clearer than usual.

Hilum shadows are not excessive, but slight

calcification is present on right side.

Diaphragm has a poor excursion, and is high.

The posterior mediastinum is not as clear as normal.

Clinical Condition During Attack. Orthopnoea is present and is extreme. The patient sits up and throws her head back. The chest looks full and fixed and remains in the inspiratory phase. The diaphragm is low, and the plurocostal sinus is obliterated. The costal margins move toward thd median line during inspiration. Signs of asphyxia are present, cyanosis with sweating, feeble pulse and cold extremities. The movements of respiration are very slow and wheezing; inspiration is short and expiration much prolonged, laboured and accompanied by a loud wheezing. Respiration is almost purely costal. In spite of active muscular efforts the chest expands but little.

The percussion note is hyper-resonant and low-pitched (Biermer's "box tone"). Inspiration is feeble, rapid, short and comparatively noiseless, expiration is abnormally loud, much prolonged and moist. Sibilant and sonorous rales obscure both phases in places. A loud wheezing is audible all the time.

Haemopoietic System.

There are no subjective phenomena.

The thyroid gland is prominent and the neck appears full. It (the gland) does not pulsate and no Bruit de Diable is heard over it.

Blood.

Size of red blood corpuscles	7.0 μ
Haemoglobin	70%
Red blood corpuscles	4,268,000
White blood corpuscles	8,320
Colour index	0.83

Differential count.

Polymorpho-nuclears	54.75%
Small lymphocytes	29.75%
Large mononuclears	10.0 %
Eosinophils	5.4 %

Arneth Count.

No. 1 type	0 %
2 type	2 %
3 type	36 %
4 type	54 %
5 type	17 %

Wassermann - negative

Van den Bergh reaction - indirect.

Blood bilirubin - 0.5 mgm per 100 c.c. plasma.

Blood calcium - 11.5 mgm per 100 c.c. plasma.

Blood sugar - 55 mgm per 100 c.c. plasma.

Circulatory System.

Pulse. Arterial wall not palpable.

Frequency 80

Rhythm regular

Wave is weak and easily obliterated.

Blood pressure - systolic 120

diastolic 80

Cyanosis has already been referred to.

Heart. No pulsation visible, except in the epigastrium.

Apex beat palpable in the sixth interspace $2\frac{1}{2}$ inches from mid-sternum.

Borders - $\frac{111}{\frac{1}{2}/2\frac{1}{2}}$

There are no murmurs.

There is an accentuation of the second sound in the pulmonary area.

X-rays show a long and narrow heart shadow; there is slight bulging of the outline in the seventh right interspace.

Posterior cardiac space is clear.

Urinary System.

No subjective phenomena.

Urine. Lemon-coloured and clear.

Two pints in 24 hours; proportion of day urine to night urine 3:1.

Specific gravity 1,010.

Acid reaction, Ph6.

Urea excretion on standard diet - 2%.

No abnormal constituents.

Deposit - nil.

Paroxysmal Urine. Reaction acid.

Specific gravity 1,022.

Ether reaction well marked.

Urine clears on heating, showing presence of urates.

Odour of ammonia very strong.

Excretion of chlorides decreased.

Alimentary System.

Appetite is fairly good.

She suffers from distension after eating and gastric flatulence.

Lips are slightly cyanosed.

Teeth are good but for a right upper lateral incisor, which has an abscess at its apex.

Gums are healthy.

Tongue is large and coated.

She does not suffer from nausea nor vomiting.

Bowels are not constipated.

Faeces. No occult blood present.

No tubercle bacilli found.

Appear normal.

Abdomen. Nothing to note.

Test meal:- total acidity 30

Free Hcl. 0.04 %

Laevulose tolerance test:-

Blood sugar does not rise above 0.12 per cent and the curve is normal.

Integumentary System.

Reaction of skin to stroking is positive.

Skin tests:- Feathers

Wheat

Delayed skin test to the organisms of the sputum:-

Streptococcus viridans)
)
Micrococcus catarrhalis) Positive.
)
Staphylococcus aureus)

Von Pirquet's tuberculin test - negative.

Reproductive System.

Catamenia began at age of 15 years.

Loss is normal in amount, but clotty.

The cycle is 4 weekly, and regular

There is left-sided one-day premenstrual dysmenorrhoea.

Nervous System.

She is of average intelligence.

She is depressed.

Sleep is good, except for attacks of asthma.

Cranial nerves - corrective glasses for astigmatism are worn.

Pupils are normal.

Other cranial nervous functions are normal.

Cervical sympathetic normal; cilio-spinal reflex very active.

Motor functions normal.

Reflexes. Superficial - decreased.

Deep - decreased.

Organic - normal.

Sensory functions are normal.

Vasomotor and trophic functions normal.

Locomotory System.

Normal.

Diagnosis.

Asthma:- Type 2 - Adults.

Subtype (b)

Treatment.

The Attack.

The hypodermic injection of ½ c.c. epinalin, as adrenalin by itself now no longer has the effect it had.

Room - quiet, warm and airy.

Brandy - ℥ss - in black coffee is given.

Hot water bottles are applied to the feet.

First week after attack.

Ephedrine hydrochloride gr. ½ at bedtime.

Potassium Iodide gr. 10 thrice daily, or eupnine 3ī morning and evening.

Blood Therapy - 4 c.c. withdrawn from the arm and immediately injected into the buttock twice during the week at equal time intervals.

Diet. Glucose - 3ī - morning and evening - in a little water on an empty stomach.

Bread avoided as much as possible.

Treatment of the Fundamental Cause.

This is a case of asthma which has followed an acute infection of the respiratory system. There are unfortunately two complications to be treated at the same time as the asthma. These are:-

1. hypertrophic emphysema;
2. enlarged mediastinal glands.

The former has begun to show itself in a rather shorter period of time than might be expected. The general aspect of the case suggests tuberculosis; but no confirmation is forthcoming and the patient remains in a more or less constant condition.

Treatment, then, has consisted of:-

1. avoidance of predisposing or exciting causes;
2. avoidance of fatigue, overwork and emotional stress;

3. attention to diet and the giving of sugar and hydrochloric acid;
4. alleviation of symptoms whenever they arise;
5. dealing with sources of irritation, such as the incisor tooth and nasopharynx;
6. the giving of an autogenous vaccine, made from the sputum and a swabbing of the naso-pharynx;
7. the treatment of the complications, namely emphysema and enlarged mediastinal gland;
8. the improving and maintaining of the general health by every possible means;
9. specific treatment.

Avoidance of predisposing and exciting causes.

Driving in open motor cars or motor coaches or riding pillion on motorcycles has been stopped. When possible, walking against a head wind has been avoided. Since treatment was instituted she has slept in a bedroom facing south.

All feather cushions, pillows and eiderdowns have been dispensed with in her home.

She has hardly ever eaten bread, as such, since it appears that toasted bread has not the same liability to upset her. Accordingly, this is taken for choice. New bread has been rigorously avoided.

Her room has been furnished very meagrely and the floors laid with linoleum, and the walls painted, the object of all being to avoid dust as much as possible. Complete avoidance is impossible from the situation of her home. For economic reasons such a situation must needs be faced.

For premenstrual dysmenorrhoea, she at first had four days treatment, with bromides and anti-pyrin. This has since been stopped as the pain ceased.

Avoidance of fatigue, overwork and emotional stress.

It was found necessary for her to give up work of any kind. She helps at home in a small way. Ten hours rest in bed each night have been enforced.

Attention to diet.

Only the lightest of meals are taken after midday. No fluid is allowed with meals; such are not taken until one hour has elapsed. No more than two courses are allowed at a meal. Vegetables have been taken chiefly in the form of purées. Reference to bread has already been made. All foods containing wheat have been taken sparingly.

Flatulence has been treated with carminatives and charkaolin.

Dilute hydrochloric acid has been given in doses of 3ss - 3i with water during meals, breakfast and lunch. This was done persistently for six weeks. Since then she has taken it whenever she had indigestion, for a week at a time.

She has been encouraged to eat sweets, particularly barley sugar, on going to bed at night.

Alleviation of Symptoms.

Insomnia has been treated with luminal-sodium gr. ½ at bedtime.

Headaches have been treated with bromides and phenazone.

For the cough, a linctus containing oxymel scillae, syrup of tolu and tinct. Camph Co. - 20 minims of each for a dose - has been most efficacious.

For the depression, she has been encouraged to keep out in the open as much as possible. A light occupation - taking a neighbour's children for walks - has been insisted on. Her illness has been carefully explained to her, for which she was very grateful.

Sources of irritation.

The incisor tooth referred to was extracted under local anaesthesia. There was a typical apical abscess.

The nasal mucous membrane was cauterized on

the affected side twice at monthly intervals.

The pharynx was painted with collosol argentum (1 in 2,000) every other night for three months.

She was taught to spray her nose and throat night and morning with Dobell's solution. This is, of course, still done, and now forms a part of her ordinary toilet.

With this irrigation and the tooth extraction, the right antrum cleared. It was not found necessary to operate on it.

Vaccine Treatment.

A mixed autogenous vaccine, containing micrococcus catarrhalis, streptococcus viridans and staphylococcus aureus was begun in Autumn 1930. The doses ranged from 5 to 1,000 million. The second doses produced a mild attack of asthma; The fifth dose causes as severe an attack as she has ever had. The dose was accordingly reduced and a smaller increase given each time. Given at weekly intervals, the course occupied 18 weeks.

Emphysema.

For the treatment of this she was sent to London. Here she had a course of compressed air baths, extending over two months. At first, they were given every four days, and gradually the intervals were shortened until she had them daily.

It is noteworthy that no attack of asthma occurred during that time.

She certainly obtained considerable relief from this treatment.

Enlarged mediastinal glands.

Treatment consisted in her being sent to Margate, during the Summer. She was able to secure light occupation there during her four month's stay.

During this time she was given syrupus ferri iodid. 3ī thrice daily.

During the Winter, cod-liver oil has been taken regularly.

General Health.

Anaemia has been vigorously treated with various preparations of iron and arsenic in systematic courses of 6-8 weeks three times a year.

Thyroid extract in ½ grain doses has been given for similar periods.

Twice a year she has been sent to the home of an aunt in Northamptonshire for a change of 2-3 weeks at a time.

She has rigorously excluded from contact, whenever possible, with persons suffering from acute infectious catarrh.

In the last year, she has been having courses of Livogen for periods of 2 months at a time, in

doses of ℥ morning and evening. This has been of great help to her. After one course, her red cell count was actually 5,240,000 per cubic mm.

Specific treatment.

In January 1930, she had a course of peptone, 5 grains thrice daily orally for 3 weeks. This was repeated a month later.

Progress Notes.

February 1930 - Asthma.

May 1930 - Dyspepsia.

October 1931 - Conjunctivitis.

State on Examination. October 1932.

There have been no further definite attacks of asthma, but occasionally she has complained of chest discomfort. Her weight is now 10 stone 4 lbs., and steady.

Thoracic expansion is now three inches.

Her blood count is now normal, except for the eosinophilia.

There are now no symptoms of indigestion.

The naso-pharynx appears healthy.

The emphysematous condition of her chest is much improved.

Cough and dyspnoea are only occasionally present.

Her general health is very good indeed.

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CASE NO. 3.

Name:- Barbara Beckett.

Age:- 40 years.

Occupation:- Upholstress.

Single.

Date of Examination:- February 28th 1929.

Complaint:- Attacks of dyspnoea, of sudden onset, occurring in the early hours of the morning, associated with wheezing and cough.

History. Personal.

As a child she was very subject to bronchitis. Peculiarly enough, she became free of bronchitis after the age of seven. These bronchitic attacks were always worse in the Winter and Spring.

In November 1925 she developed influenza, convalescence from which was exceedingly slow. Indeed, it is difficult to state exactly when she had her first attack of asthma; for she began to suffer from a kind of wheezing at night after the influenza. Gradually this wheezing and cough has developed into definite attacks of asthma. So the onset has been very gradual and has undoubtedly followed the influenza.

It now takes 3-4 weeks for her to get over the

cough and chest discomfort following an attack. Following this there is generally an interval of about a month before she has another attack. In the Summer, she remains comparatively well.

(a) Factors influencing an attack.

The attacks are always worse and more frequent in February and March. She finds she is much more comfortable at the seaside; indeed, she has never had an attack there. She has, however, enjoyed best health at Redcar. She has never had an attack whilst at work. Nor is she affected by household dusts. There is no doubt that "heavy suppers" bring on an attack.

(b) Nature of the attack.

Certain prodromata occur before an attack. These are:-

itching of the eyes;

tightness in the throat.

The attacks occur suddenly between 3 and 4 o'clock in the morning, when the patient wakes up choking with loud wheezing. It lasts about one hour and is followed by a troublesome cough. At such times as she has acute coryza ("colds"), the asthmatic attacks occur almost nightly. A drink of water gives relief at the time of an attack.

She is much easier once the cough develops. This cough is paroxysmal and relieved by the expectoration of sputum. Wheezing is loud and audible during the attack. Coryza is not a marked symptom. She also suffers from pains at the lower end of the sternum during an attack.

(c) Health between attacks.

For the last five years she has suffered from increasing dyspnoea on exertion. This is definitely worse in cold weather.

(d) Other diseases.

Past	Measles	5 years old
	Pertussis	6 years old

N.B. She suffered from bronchitis before she had either of these.

	Influenza	1918
	Haemorrhoids	1925
	Conjunctivitis	1926
	Laryngitis	1928
	Facial neuralgia	1929
	Hysteria	1930
Present.	Haemorrhoids.	

(e) Other Allergy.

Past.	Urticaria	1917
	Migraine	1906 - 1912
Present.	None.	

History. Family.

Antecedents. Father died of gastric carcinoma.

Mother died of "chest trouble".

Contemporaries. One brother died of pulmonary tuberculosis.

Family History of Allergy.

Antecedents. Mother had asthma.

Contemporaries. Nil.

History of Previous Treatment.

This has consisted of the inhalation of Potter's powder for the relief of the attack. They have now lost their effects and seem to suffocate her.

Lobelia and various cough mixtures have been the treatment of symptoms following the attack.

External Particulars of Home.

Her home is on clay soil, on low ground. She lives in a closed locality, a short thickly-populated street, with a continuous block of houses on either side. It is not a bus route, but a popular parking place for vehicles of all descriptions. There is a small garden at the back of the house. The house is within two hundred yards of a brewery. The atmosphere is frequently laden with the odour of hops, etc. from this brewery. The street runs east and west

and is exposed to winds.

There is one other case of asthma a few doors away.

Internal Particulars of Home.

She has lived in her present residence for 25 years. The house is damp, and heated by coal and wood fires. The floor is wood on cement foundations. Six rooms are in use, which are not crowded with furniture. One plant is kept indoors - an aspidistra - in the sitting room. Lighting, window space and ventilation are poor. The windows are kept open day and night. The floors are covered with linoleum, there being no carpets. Sweeping is the method of cleaning. The walls are all papered.

	Horsehair.	Feathers.	Flock.	Kapok.
Cushions.	0	+ +	0	0
Bedding	+	+	+	0
Pillows	0	+ +	0	0
Upholstery	+	0	0	0

Feather eiderdowns are used.

In patient's own room are feather cushions, mattress and pillows, with eiderdown.

One cat is kept.

State on Examination.

She is of average intelligence.

Height - 5 feet 1 inch

Weight - 10 stone 7 lbs.

Development normal, but fat.

General appearance is healthy, but inclined to be plethoric.

Attitude - very interested in the examination and is easily impressed.

Temperature is normal.

Respiratory System.

Subjective Phenomena.

Cough - worse in the early morning - loose and followed by expectoration of yellowish green sputum in lumps. This cough is different from that which occurs during an attack. This latter follows the wheezing, is paroxysmal and followed by expectoration of frothy tenacious sputum.

Dyspnoea. This has been present 3-4 years, and follows hurry and exertion. It is quite different from that which occurs during an attack, which is paroxysmal and obstructive in type. There has been no haemoptysis. Chest pains occur during an asthmatic attack at lower end of sternum; a dull ache, relieved when attack passes off.

Breathing. Costal in type.

Twenty per minute.

Regular and uniform in rhythm, but exaggerated.

Sputum. This is farily abundant, and green-

ish yellow in colour. It is only frothy during a paroxysm. Usually, it is expectorated in lumpy masses. Cough is relieved by its discharge. Microscopically, it contains of Charcot-Leyden crystals, eosinophils and micro-organisms. Curschmann's spirals are not present. On cultivation, the micro-organisms are proved to be streptococcus viridans and micrococcus catarrhalis. Tubercle bacilli are not detected.

Naso-Pharynx. Nose is straight but high and narrow. The alae nasi do not move on inspiration, but the mouth is kept open. The nasal septum has a marked deviation to the left. The left turbinate is swollen and boggy looking.

The pharynx is red and congested and studded with granulations, with catarrhal discharge from posterior nares. Uvula is short. Tonsils are buried; right one has a small hard concretion present. Transillumination shows opaque frontal sinus.

Thorax.

Inspection.

Normal in outline and well-formed, particularly in the infraclavicular regions.

Measurements.

Anteroposterior diameter	8 inches.
Transverse	9½ inches.
Circumferance	33 inches

Thoracic Index 84

Expansion 2 inches.

Subcostal angle 65°

Movements are uniform and good in the upper half of the chest; in the lower half they are of greater magnitude on the left. Litten's diaphragmatic sign is present; on the left normal, but diminished in extent on the right side.

Palpation. Confirms inspection regarding form and movements. Vocal fremitus is normal, except in the right infrascapular region, where it is decreased.

Percussion. Kronig's isthmus measures at narrowest point -

both sides - 1½ inches.

Percussion note is normal, except in right infrascapular region, where it is duller than normal. Sense of resistance to percussion is increased in the right infrascapular region.

Tidal percussion is:-

Right - 1½ inches.

Left - 2 inches.

Auscultation. The breath sounds are vesicular in type generally, except in the right infrascapular region, where they are barely audible. Inspiration bears to expiration the normal 3:1 ratio.

There are no accompaniments.

Vocal resonance is normal, except in the right infrascapular region where it is decreased.

X-rays.

Diaphragm is higher and excursion better on left side than on right.

Hilum shadows are moderate in extent; some calcification is present.

Posterior mediastinum is clear.

There is no evidence of tuberculous infiltration.

Clinical condition during attack of asthma.

She awakes from sleep with a feeling of suffocation. She sits up in bed and fixes her arms, so as to bring into action all possible muscles of respiration. Respiration is laboured and difficult and slow, inspiration being short whilst expiration is greatly prolonged. Both are accompanied by loud wheezing sounds, audible at a distance. She is pale, but the lips are dusky and the expression is anxious and distressed. The jugular veins are distended and prominent. The accessory muscles of respiration are seen to be in violent action, notably the sterno-mastoids, scalenes and pectorals. The skin is moist. The chest is much distended. The supra-clavicular and lower costal margins are sucked in at inspiration.

Percussion reveals marked hyper-resonance and encroachment on the cardiac and hepatic dullness. Inspiration is short and high-pitched, expiration very prolonged. Abundant sonorous and sibilant rhonchi obscure the breath sound in different areas. The pulse is small, quick and irregular.

A distressing paroxysmal cough follows the wheezing. This is relieved by expectoration of some frothy sputum, whereupon the dyspnoea soon subsides.

Haemopoietic System.

No subjective phenomena.

Lymphatic vessels and glands - nothing abnormal.

Ductless glands - nothing to note.

Blood.

Size of red corpuscles	7.3 μ
Haemoglobin	85%
Red corpuscles	4,480,000
White corpuscles	10,420
Colour Index.	0.96.

Differential Count.

Polymorpho-nuclears	54.3%
Small lymphocytes	31.3%
Large mononuclears	8.6%
Eosinophils	5.6%

Arneth Count.

No. 1	Type	1%
	2 Type	16%
	3 Type	38%
	4 Type	37%
	5 Type	8%

Wassermann - negative

Van den Bergh reaction - indirect.

Blood bilirubin - 0.3 mgm per 100 c.c. plasma.

Blood Calcium - 10 mgm per 100 c.c. plasma

Blood sugar - 60 mgm per 100 c.c. plasma.

Circulatory System.

There are no subjective phenomena to be solely attributed to this system.

Pulse. Arterial wall is not palpable.

Frequency - 78

Rhythm is regular

Pulse wave is normal in character.

Blood pressure - systolic 140

diastolic 80

Heart. Left mamma obscures praecordial region.

Apex beat is not visible.

No abnormal pulsations visible.

On palpation, apex beat is felt in fifth interspace 3 inches from mid-sternum.

Borders - 111

There are no murmurs.

The pulmonary second sound is accentuated.

X-rays show a normal heart shadow.

Posterior cardiac space is clear.

Urinary System.

No subjective phenomena.

45 ounces in 24 hours; proportion of day urine to night urine 3:1.

Specific gravity 1,015.

Acid reaction Ph. 6.7

Urea excretion on anstandard diet - 2%

No abnormal constituents.

No deposit on standing.

Paroxysmal urine.

Reaction acid.

Specific gravity 1,020

Ether reaction positive.

Urine clears on heating, showing presence of urates.

Excretion of chlorides decreased.

Smell of ammonia very strong in urine.

Alimentary System.

She complains of heart burn at times, which occurs about 15 minutes after meals and is relieved by hot water and bismuth.

Teeth. Wears complete upper denture.

No lower molars and premolars; only

incisors and canines, which are in poor condition.

Gums.

Bleed on palpation at insertion of lower teeth.

Tongue is large and flabby, and crossed by various fissures. Vomiting has only occurred once, during an attack of asthma which it appeared to relieve.

She does not suffer from constipation.

Faeces.

No occult blood present.

No tubercle bacilli present.

Abdomen.

Abdominal walls healthy

Nothing abnormal found.

Test meal:- total acidity - 47

free hydrochloric acid - 0.08%

Laevulose tolerance test:-

blood sugar does not rise above 0.13 Per cent, and the curve is normal.

Integumentary System.

Reaction of skin to stroking - negative

Skin tests negative.

Delayed skin test to micrococcus catarrhalis and streptococcus viridans, of the sputum - positive.

Von Pirquet's tuberculin test - negative.

Reproductive System.

Catamenia began at 14½ years of age.

Cycle is 4-weekly.

Loss is normal in amount and quality

No abnormal discharge.

Nervous System.

Higher cerebral and mental functions.

She is emotional and impressionable, otherwise there is nothing to note.

Cranial nerves.

Glasses are worn - Right + 4 D

Left + 3 D

Pupils react normally.

Fundi are normal in appearance.

Cervical Sympathetic.

Nothing to note.

Motor functions.

Are normal.

Reflexes. Normal.

Vasomotor and trophic functions.

Nothing to note.

Locomotory System.

Normal.

Diagnosis.

Asthma:-

Type 1 - Adults.

Subtype (b)

Treatment.

The attack.

The hypodermic injection of 0.25 c.c. of Liquor Adrenalin hydrochloride.

Room warmed, well ventilated and quiet.

Small cup of strong black coffee given.

Back rubbed with unguent capsicum.

Hot-water bottles applied to feet.

Magnesium sulphate -3ʒ- in warm water.

Diet.

Fluids only till free from symptoms - in small quantities every two hours.

One week following attack.

Ephedrine hydrochloride gr. ½ at bedtime.

Potassium Iodide gr. 10 thrice daily.

Magnesium sulphate 3ss each morning

Blood Therapy.

4 c.c. withdrawn from the arm and immediately injected into the buttock twice during the week at equal intervals.

Glucose:- 3i morning and evening, in water, on an empty stomach.

Treatment of the Fundamental Cause.

This will considered under the various headings:-

(a) Avoidance of predisposing or exciting causes.

This patient's attacks of asthma are very

often heralded by an acute infectious catarrh - the so-called "cold". To combat this menace, the following measures have been adopted:-

1. strict avoidance of all persons with "colds";
2. monthly injections - from September till April - of a prophylactic anticoryza vaccine, namely Burroughs and Wellcome's No. 4;
3. regular spraying and douching of the nose and throat with Dobell's solution twice daily, night and morning.

These "colds" are notoriously more common in the Winter and Spring. It is during these seasons she has her attacks. She was advised to have her holiday in September or October, at the sea, if possible; the object of this is to enable her to be in as fit a condition as possible to face the Winter and Spring.

She was adivsed to avoid going to places of entertainment, such as cinematograph theatres, in these seasons. Exercise in the open air - for example, walking - was encouraged.

She was urged not to sit in draughty places nor to delay in changing footwear when wet.

(b) Attention to diet.

She was advised to make the midday meal her biggest of the day. Only light suppers are taken.

Bearing in mind the condition of her teeth, her attention was particularly drawn to having her food so prepared so as make up for the loss of her own teeth, namely meat to be minced, cut up into small portions and so on, and vegetables to be taken as purees. At the same time the necessity of the proper mixing of the food with the saliva was pointed out to her.

The importance of appropriate rest after meals and avoidance of hurrying over meals was explained.

The fat in her diet was reduced.

(c) Alleviation of symptoms.

Every method was made to abort a "cold" by

1. obtaining free diaphosesis:-
   (i) confinement to bed;
   (ii) wrapping in warm blankets;
   (iii) hot drinks;
   (iv) quinine hydrochloride gr. 5 and aspirin gr. 10, or Dover's powder gr. 10 for 3-4 doses, every 2 hours.
2. the use of a nasal atomiser, with menthol and eucalyptol, frequently.

After the early stage, spraying or douching the nares 3-4 times a day with warm saline or Dobell's solution was carried out.

Indigestion was promptly treated with calomel and podophyllin, as an apperient, and magnesium carbonate and carminatives.

She was 35 pounds above the average weight for her size and age. The dyspnoea was partly due to this adiposity.

Her Basal Metabolic Rate was - 18.6

The treatment of this obesity consisted:-

1. in correct dieting, starting was a 1,400 calorie diet and gradually increasing this to 1,800;
2. the exhibition of thyroid extract in doses of ½ grain morning and evening.

Gradually her weight was reduced by 14 lbs., when her condition was very much improved generally. Strict dieting was then relaxed; but butter, cream, the fat of meat, and especially that of ham and bacon were to be avoided as much as possible. The thyroid was continued in one ½ grain dose daily. Her weight has since remained fairly constant. Outdoor exercise has been encouraged.

To overcome the inclination to become self-centred, her illness was explained to her, special stress being laid on the dependence of her prognosis on her own individual efforts.

A saline cough mixture was prescribed for the early morning cough, when present. This consisted

of 10 grains of sodium bicarbonate and 3 grains of sodium chloride in one ounce of aqua chloroformi to be taken in the mornings.

(d) Sources of Irritation.

The remaining teeth in the lower jaws were extracted. The tonsils were dissected out, the naso-pharynx curetted and a sub-mucous resection done on the nose. Since then the nose and throat have been sprayed daily with Dobell's solution. The frontal sinus has lost its opaqueness to trans-illumination.

(e) Vaccine treatment.

A mixed autogenous vaccine, containing streptococcus viridans and micrococcus catarrhalis was administered. The doses ranged from 5 to 1,000 million, given at weekly intervals, in twelve injections.

(f) Chronic Pleurisy of Right Side.

She has been advised to sleep and lie on her left side.

When pain has been present, this has been treated with radiant heat daily until relieved.

(g) General Health.

In the last year she has been having courses of Livogen for periods of 2 months at a time, in doses of 3ℸ morning and evening.

Progress Notes.

March 1929 - neuralgia of the face.

August 1930 - hysteria.

March 1931 - laryngitis.

State on examination - October 1932.

No further attacks of asthma have occurred since completing treatment.

She now weighs 9 stone 5 lbs., and her diet is restricted only in the fat constituent. Over-eating is avoided.

Her naso-pharynx is healthy.

Her chest expansion is three inches.

Her blood count is normal except for the eosinophilia.

There are no symptoms of indigestion.

She remains remarkably free from "colds".

Cough is only experienced occasionally.

The pain in her right side has not worried her any further.

Her general health is very much improved.

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CASE NO. 4.

Name:- George M.

Age:- 21 years.

Occupation:- Lorry Driver.

Single.

Date of Examination:- June 17th, 1931.

Complaint:- Attacks of dyspnoea of sudden onset, occurring at one time about 7 a.m. and now on going to bed about 11 p.m. It is accompanied by wheezing and a feeling of suffocation, and is followed by a cough.

Duration:- 1½ years.

Onset:- July 1930.

History. Personal.

In July 1930, the patient received orders to proceed to a farm to pick up his load. He reached the farm at various times between 7.30 a.m. and 9.30 a.m. He noticed that he became tight in his chest and wheezy whilst he was in the farm yard; but beyond a slight cough his symptoms soon disappeared after leaving. He attributed his symptoms to the smells and did not pay much attention to them. They did not occur again after the week he was occupied

a sensation of fullness in the throat; and

a tickling of the roof of the mouth.

The time and places when the attacks occur are well brought out in the history.

The duration of the attack was varied, in one year lasting only when he was in the farmyard and in the next lasting the ten hours at night.

The attack was mitigated but not stopped by giving ephedrine before going to bed.

Coryza was hardly present at all.

Wheezing was very marked and persistent.

Pains in the sternum came on some time after the attack started. Such pains were of a dull aching character and limited to the sternum.

Cough was paroxysmal, and relieved as stated.

Dyspnoea was a marked symptom.

So that this latter and the wheezing are the predominant factors in the attack.

(c) Health between attacks.

This is very good indeed.

He is not particularly subject to "colds".

(d) Previous Illnesses.

Pneumonia when 6 months old.

Measles at the age of 7 years.

Varicella at the age of 5 years.

Influenza January 1931.

(e) Other Allergy.

None.

History. Family.

Father - 53 - alive and well.

Mother - 52 - " " " ; used to have fainting fits.

One brother died from poliomyelitis (?)

Three sisters and another brother alive and well.

Family history of Allergy.

Antecedents.

Mother - migraine

Maternal antecedents - asthma

urticaria.

Contemporaries.

None.

History of Previous Treatment.

In 1930, he did not see a doctor at all. In 1931 his attacks were relieved by adrenalin given at the time and by removal from contact with the specific allergen.

External particulars of Home.

The house stands on gravel soil, on fairly high ground in an open locality. It is in a fairly busy thoroughfare, which is a bus route. It has a garden and is near disused stables. There is an occasional odour from a nearby cesspool.

There is another case of asthma about three doors away, in a man, aged 60.

Internal particulars of Home.

The patient has lived in his present home all his life. It is quite dry. Coal is used for fires, and gas for lighting and cooking. The floor of the house is wood on cement.

Six rooms are used which are crowded with furniture.

One plant - a fern - is kept in the house.

The house is well lighted with moderate window space and ventilation. Windows are kept open day and night. There is very little dust, and the cleaning methods consist of sweeping and washing.

Carpets, linoleum and rugs are all used in the house. The walls are papered, but in the kitchen distempered.

	Horsehair.	Feathers.	Flock.	Kapok.
Cushions.	—	+	+ +	—
Bedding.	—	—	+ +	—
Pillows.	—	+	+	—
Upholstery.	+	—	+ +	—

Feather eiderdowns are used.

No pets are kept.

In the patient's room there was a feather eiderdown and feather pillows, flock bedding and a horsehair upholstered chair.

State on Examination.

He is of average intelligence.

His height is 5 feet 10 ins.

His weight is 10 stone 7 lbs.

Development is good.

General appearance is lethargic, and facial expression rather listless.

There is no obvious morbid appearance, and no evidence of previous disease.

His temperature is normal.

Respiratory System.

Subjective phenomena.

Cough. This is not a prominent symptom. It is only present towards the end of an attack of dyspnoea and wheezing. It is paroxysmal in nature and relieved by the expectoration of a little tenacious sputum.

Dyspnoea. This is the most pronounced symptom. It is associated with a feeling of suffocation and is accompanied by audible wheezing. It is only present during an attack.

Sternal pains, also occur during an attack. They soon pass off after the attack is over. They are of a dull aching character, and do not radiate laterally.

A feeling of suffocation is quite a characteristic of his attacks. It arises with the dyspnoea, but passes off sooner, in fact at the time when the cough begins.

Breathing. Abdominal or diaphragmatic in type.

Costal margins diverge on inspiration.

Eighteen per minute.

Regular in rhythm.

Sputum. This is scanty.

It is greyish in colour and frothy, and expectorated after much exertion.

Microscopically, it contains eosinophils, Charcot-Leyden crystals and Curschmann's spirals, along with micro-organisms. On culture the latter are found to be micrococcus catarrhalis, streptococcus viridans and haemolytic streptococcus longus. Tubercle bacilli are not found.

Naso-pharynx.

Nose is straight but high and narrow.

The alae nasi do not move on inspiration.

The nasal septum is straight.

Right inferior turbinate is swollen; and the right side of the frontal sinus is obscured on transillumination.

The throat is narrow.

Uvula is small and twisted to the left.

Tonsillar beds are occupied by small masses of adenoid-like tissue.

Thorax.

Inspection.

Funnel shaped in type.

Shoulders are rounded.

Measurements.

Anteroposterior diameter	8 inches.
Transverse	10½ inches.
Circumference	33 inches.
Thoracic Index.	80
Expansion	3½ inches.
Subcostal angle	82°

Movements are uniform and good.

Diaphragmatic movements are normal.

Litten's diaphragmatic sign is present.

Palpation.

Confirms inspection as to movements and form.

Vocal fremitus is normal.

Percussion.

Kronig's isthmus measures at narrowest point. right - 1½ inches; left - 2 inches.

Percussion note is normal, except:-

1. in right infraclavicular region, when it is more resonant than normal;
2. in the interscapular region where it is duller than normal.

The sense of resistance to percussion is normal except in the interscapular region, where it is greater than normal.

Tidal percussion is 1½ inches on both sides.

Auscultation.

Vesicular in type, generally.

It is bronchovesicular in the right supra-clavicular region and over the sternum near the angle of Louis.

It is bronchial close to the spine on each side in the interscapular region.

It is harsh vesicular in the right supra-scapular and right superior axillary regions.

There are no accompaniments.

Vocal resonance is normal.

D'Espine's sign, or the presence of whis-pered pectoriloquy over the spinous processes of the fourth and lower thoracic vertebrae, is present.

X-rays.

The apices are clear.

Hilum shadows are extensive, with a moderate degree of calcification.

Branching linear shadows are moderately extensive.

There are no signs suggesting active tuberculosis.

Clinical condition during an attack.

Orthopnoea is present.

There is cyanosis and sweating, with cold extremities.

The chest is full and fixed.

Respiration is very laboured.

Inspiration is short and expiration prolonged.

Loud, audible wheezing sounds are present both with inspiration and expiration.

All the extraordinary muscles of respiration are being employed.

The diaphragm is low.

The pleurocostal sinus is obliterated.

On percussion, the chest is markedly hyperresonant. The cardiac and hepatic dullness is

encroached upon.

Abundant and flitting rhonchi are present.

The cough is very persistent and distressing once it begins.

Haemopoietic system.

No subjective phenomena.

Lymphatic vessels and glands - nothing to note.

Ductless glands - nothing to note.

Blood.

Size of red corpuscles.	7 μ
Haemoglobin.	90 per cent.
Red corpuscles	5,890,000
White corpuscles.	9,280.
Colour index.	0.8
Differential Count.	
Polymorpho-nuclears	49.3%
Small lymphocytes	30%
Large mononuclears	15.3%
Eosinophils	5.4%
Arneth Count.	
Type 1	3.5%

Type 2 17%

Type 3 36%

Type 4 30%

Type 5 12.5%

Wassermann - negative.

Van den Bergh - indirect.

Blood bilirubin - 0.35 mgm. per cent.

Blood Calcium - 11 mgm. per cent.

Blood sugar - 57 mgm. per cent.

Circulatory System.

No subjective phenomena.

Pulse. Arterial wall is not palpable.

Frequency - 78

Sinus arythymia is well marked.

Pulse wave is normal.

Blood pressure - systolic 110

diastolic 80

Heart. Apex beat is not visible.

No abnormal pulsation visible.

On palpation, apex-beat is located in 5th interspace, 3½ inches from sternum.

Borders $\frac{\text{III}}{1/3\frac{1}{2}}$

There are no murmurs.

The pulmonary second sound is accentuated.

X-rays show normal heart and aortic shadows, and a clear posterior cardiac space.

Urinary System.

No subjective phenomena.

Urine. Orange colour.

Quantity in 24 hours - 50 ozs.

Proportion of day to night urine, 4:1

Specific gravity - 1,015.

Acid reaction - Ph. 6

Urea excretion on standard diet = + 2%

No abnormal constituents.

Deposit of phosphates on standing.

Paroxysmal Urine.

Reaction acid - Ph 6.5

Specific gravity - 1,025

Ether reaction positive.

Urates present.

Chlorides decreased.

Smell of ammonia present.

Alimentary System.

No subjective phenomena.

Teeth - two lower molars are decaying.

Gums - are red at teeth margins.

Vomiting - occurred in January 1930

associated with abdominal pain and diarrhoea. There is no constipation.

Faeces. No occult blood present.

No tubercle bacilli found.

Abdomen. Nothing to note.

Test meal:-

Total acidity = 46

Free hydrochloric acid = 0.08%

Laevulose tolerance test:-

blood sugar does not rise above 0,12% and the curve is normal.

Integumentary System.

Reaction of skin to stroking - positive.

Skin Tests:-

Horse dandruff +

Cow hair +

Tobacco ±

Delayed skin tests to the micro-organisms of sputum - negative.

Von Pirquet's tuberculin test is negative.

Reproductive system.

Nothing abnormal.

Nervous System.

Higher cerebral and mental functions.

Intelligence - average.

He is listless.

Speech is slow but normal.

Cranial nerves.

Nothing abnormal.

Cervical sympathetic.

Pupils react normally.

Cilio spinal reflex is absent.

Fundi are normal.

Motor functions.

Are normal.

Reflexes.

Normal.

Vasomotor and Trophic functions.

Normal.

Locomotory System.

Normal.

Diagnosis.

Asthma:-

Type $\bar{1}$. - Adults.

Subtype (a)

Treatment.

The Attack.

The hypodermic injection of 0.25 c.c. of liquor adrenalin hydrochloride.

Strong black coffee in small quantity.

Back rubbed with unguent capsicum.

Hot-water bottles applied to the feet.

Patient was moved to another warm, but well-ventilated room, on the last occasion.

First week after attack.

Ephedrine hydrochloride gr. ½ at bedtime.

Potassium iodide gr. 10 thrice daily.

Blood Therapy.

5 c.c blood withdrawn from arm and immediately injected into buttock once.

Diet.

Glucose -3i- morning and evening - in a little water on an empty stomach.

Treatment of the Fundamental Cause.

This was carried out under the following routine:-

(a) avoidance of predisposing and exciting causes;

(b) avoidance of overwork;

(c) dealing with sources of irritation;

(d) treatment of the complications;

(e) maintenance of the general health;

(f) specific treatment.

(a) Avoidance of Predisposing and Exciting Factors.

The history and skin tests demonstrate susceptibility to horse dandruff and cow hair.

Accordingly he was forbidden to enter a farm yard or stable, or to handle in his work anything connected therewith. It is interesting to recall that six months later, after specific treatment and this avoidance, his skin tests were completely negative to either of the above factors.

Smoking was stopped, and he was advised to avoid rooms in which smoking was habitually done.

All articles containing horse hair or cow hair were removed from his room. It is interesting to learn that, on careful investigation, the incidence of his week's attack followed immediately upon the cleaning out of his room and the placing there of a new chair, the seat of which was found to be stuffed with very dusty horse hair.

(b) The avoidance of overwork.

Following the week's attack he was given a month's holiday from work, which fortunately for both himself and his employers coincided with a slack period.

(c) Dealing with sources of irritation.

The right inferior turbinate was cauterized. The nose and throat were sprayed twice daily with Dobell's solution for six months. Since then this is done every morning. The two molar teeth concerned have been attended by a dental surgeon, one being extracted and the other having a cavity filled. The gums have been also treated by the dental surgeon, and are now healthy.

(d) Treatment of the complication.

This complication consists of enlarged mediastinal glands.

A liberal diet, with extra milk, cream and butter, was ordered.

Cod-liver oil during the Winter and Spring and the syrup of iodide of iron during the Summer and Autumn was prescribed.

He was recommended to take his holidays at Margate.

(e) Maintenance of the General Health.

He was advised to continue his occupation as a lorry-driver, and to keep in the open air as much as possible.

The administration of cod-liver oil and iron has already been referred to.

He was advised to have "colds" systematically treated.

(f) Specific treatment.

This consisted of desensitisation with a mixture, consisting of horse dandruff and cow hair, prepared by Duncan and Flockhart. The strong stock solution was diluted 1 in 10, 1 in 100, 1 in 1,000, 1 in 10,000 and 1 in 100,000. The skin was then tested intradermally with these various strengths. Using ½ c.c. intradermally, a positive reaction, about an inch in diameter, was obtained with solutions up to the 1 in 10,000 solution. Accordingly, weekly injections of this solution were given, starting with 0.1 c.c. and

doubling the dose each week. In this way, each strength solution was given, the whole course occupying just over four months.

Progress Notes.

February - dyspnoea.

No further attack of asthma has occurred.

State of examination - October 1932.

The patient now weighs 11 stone 7 lbs.

The naso-pharynx is healthy.

Eosinophilia is still present.

Skin tests to animal hair are now negative.

His general health is now excellent.

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CASE NO. 5.

Name:- Wenda R.

Age:- 2 years.

Date of Examination:- August 12th 1931.

Complaint:- Mother states that the child is attacked about 2 a.m. with dyspnoea and wheezing and extreme restlessness, followed later by a cough.

Duration of illness:- 1 year.

History:- Personal.

On the morning of the 10th August 1931, the child sneezed many times and the nose began to run like an ordinary cold.

About six o'clock in the evening her nose symptoms got much better and her eyes, which had been very red, became clearer. Then she began to wheeze.

About 2 a.m. the wheezing was at its worst and was accompanied by extreme dyspnoea and restlessness. An hour later she began to cough and her other symptoms to abate. She did not expectorate anything but a little frothy mucous. Gradually she fell asleep. She woke up about 7 a.m. and immediately began to cough again, but

with no sputum. One hour after a light breakfast, the wheezing reappeared. This, however, was never as bad as during the night and passed off in about an hour. The child did not really get well for about three days.

A week later she had another similar attack.

(a) Factors influencing an attack.

Both attacks have followed putting the child in her perambulator in an outhouse, in which was stored articles of furniture and so on, not wanted in the house.

It was also noticed that the child suffered from a "running nose" whenever she began to cut a tooth.

As an article of diet, she has never been fond of milk.

(b) Nature of the attack.

Certain prodromata are present. These are:-

1. sneezing; and
2. itching and "running of the nose".

These prodromata have appeared in the morning and lasted more or less till evening, when the asthmatic paroxysm began, with wheezing and dyspnoea. Cough appeared about 3 a.m., when other symptoms quietened. This lasted about an hour intermittently, and was followed by sleep.

Wheezing is the most prominent symptom of the attack.

Coryza is a conspicuous symptom, particularly in the prodromal stage. The cough is not severe.

There is very little sputum, of a frothy greyish nature, which is usually swallowed.

Vomiting, on one occasion, followed a paroxysm of coughing and relieved the asthmatic attack.

The child passed much urine during the attack.

(c) Health between the attacks.

This has been very good.

(d) Other diseases.

Pneumonia when six months old.

(e) Other Allergy.

None.

History. Family.

Father - 35 years old - alive and well.

Mother - 32 years old - alive and well.

Two sisters- 8 and 4 years - alive and well.

Allergy in Family.

Maternal - Grandmother - Migraine.

Mother - Urticaria.

Aunt - Migraine.

Paternal - Grandfather - Asthma.

Father - Asthma.

Contemporaries - cousin - Asthma.

History of previous treatment.

This has been symptomatic, consisting of expectorants and lobelia.

General surroundings at home.

The house is semi-detached and not kept clean. The father has been out of work for some time.

External particulars of home.

The house is on clay soil, in quite a high and open locality, in a quiet thoroughfare.

There is a small garden.

There are no stables, factories nor works for many miles around.

There is another case of asthma, in a child also, within 50 yards.

The atmosphere is clear.

Internal Particulars of Home.

Patient was born in her present home.

The locality is fairly dry, but inclined to be foggy. The house is heated by coal and wood fires.

Six rooms are used which are not crowded with furniture.

Three plants - aspidistras - are kept indoors.

Window space and ventilation is satisfactory. Windows are kept open day and night.

Very little dust occurs.

Dusting and polishing are the methods of cleaning.

There are no carpets, only rugs and linoleum.

	Horsehair.	Feathers.	Flock.	Kapok.
Cushions	—	—	+	—
Bedding	+	—	—	—
Pillows	—	++	—	—
Upholstery	—	—	+	+

There are no feather eiderdowns.

The patient sleeps on a feather pillow and hair mattress.

No pets are kept.

State on Examination.

She is of average intelligence.

Height 2 feet 10 inches.

Weight 2 stones.

Development is normal.

General appearance very contented.

No obvious morbid appearance.

Temperature is normal.

Respiratory System.

Subjective Phenomena.

Cough. Apart from that which occurs during the attack, the child has had a loose cough since her attacks. It is usually worse at bedtime and first thing in the morning. It is accompanied by the expectoration, on occasions, of a little yellowish sputum.

The cough of the attack is definitely

paroxysmal and may be followed by vomiting. What sputum there is is very scanty, greyish and frothy. The cough follows the wheezing and dyspnoea, and is itself usually followed by sleep.

Dyspnoea occurs at the beginning of an attack. It is obstructive and expiratory in type, of sudden onset, accompanied by audible wheezing, and followed by a cough.

Pain. The mother thinks that during an attack the child has epigastric pain.

Breathing. 32 per minute.
Predominantly costal in type.
Rhythm is irregular.

Sputum. Scanty and tenacious.
Greyish-yellow in colour.

It contains eosinophils, Curschmann's spirals and innumerable cocci, which on cultivation prove to be micrococcus catarrhalis and streptococcus viridans.

No tubercle bacilli present.

Naso-pharynx. The child is at present a mouth-breather and there is muco-purulent discharge from the nares, which are reddened and tender.

The nasal mucous membrane is swollen and red generally.

The tonsils are swollen and red, but do not exude pus. The anterior pillars are congested.

The pharynx is similarly congested, and shows muco-purulent discharge from the posterior nares.

Thorax. The chest is round in shape.

Measurements.

Anteroposterior - 5 inches.

Transverse - 5 inches.

Circumference - 19 inches.

Thoracic index - 100

Expansion - 1 inch.

Subcostal angle - 100°

The movements of the chest are uniform but jerky and irregular; most movement occurs in a vertical direction.

Litten's diaphragmatic sign is not present.

On palpation, the vocal fremitus is found to be decreased generally.

On percussion, the note is one of exaggerated vesicular resonance; that is, there is an increase in all the normal qualities of the normal vesicular note. The note is clearer and of a somewhat lower pitch.

It was not possible to determine tidal percussion.

On auscultation, it is very noticeable the length of time the child can hold her breath. There is decided inversion of the respiratory rhythm. Harsh, puerile breathing is present generally, except at the right apex and in the

interscapular region where it is almost bronchial. A few flitting rhonchi are heard in various regions from time to time.

Vocal resonance is loud over the whole chest.

X-ray examination snows clear lung shadows and hilum shadows, a small diaphragmatic excursion and a clear posterior mediastinum.

Clinical condition during an attack.

The child refused to stay in its bed and had to be held on her mother's knees. There she was restless and tossing her head about from side to side. Her chest was full and fixed and remained chiefly in the inspiratory position. The costal margins during inspiration moved toward the median line. She was cold and clammy. There was loud audible wheezing. The movement of the chest was up and down. On percussion, the note was markedly hyper-resonant and low-pitched. Sibilant and sonorous rhonchi were present, along with the loud wheezing.

Haemopoietic System.

There are no subjective phenomena.

Some small discrete lymphatic glands are palpable in both posterior triangles of the neck.

Thymus. There is unusual dullness over the manubrium sterni. This gland is largest at the age of this child. There are, however, no

symptoms suggesting any pressure on the trachea and blood vessels of the neck.

Blood.	Haemoglobin	85%
	Red blood corpuscles	5,170,000
	White blood corpuscles	12,000
	Colour index.	0.8.
Differential count.		
	Polymorpho-nuclears	28%
	Small lymphocytes	61.3%
	Large Mononuclears	5.3%
	Eosinophils.	5%
	Basophils	0.3%
Arneth Count.		
	Type 1	6%
	Type 2	8%
	Type 3	48%
	Type 4	33%
	Type 5	5%

Wassermann - negative.

Van den Bergh reaction - negative.

Blood bilirubin - 0.28 mgm. per cent.

Blood calcium - 9.75 mgm. per cent.

Blood sugar - 78 mgm. per cent.

Circulatory System.

No subjective phenomena.

Pulse. Arterial wall not palpable.
Frequency 120
Sinus arythymia present.
Arterial wave normal in character.
Blood pressure - systolic 80
diastolic 40.

Heart. Praecordial region normal in contour.
No abnormal pulsations visible.
The apex beat is in the 4th interspace, two inches from the mid-sternum.
Borders - $\frac{\overline{111}}{\frac{1}{2}/2}$
There are no murmurs.
X-rays show a normal heart shadow with a clear posterior cardiac space.

Urinary System.

No subjective phenomena.

Urine. Orange colour, clear.
16 ounces in 24 hours.
Specific gravity 1,024.
Acid reaction, Ph 6.
No abnormal constituents.
No deposit.

Paroxysmal Urine. Amount increased, but impossible of collection.
Reaction Acid.

Specific gravity 1028

Ether reaction present.

Urates present.

Odour of ammonia marked.

Chlorides decreased.

Alimentary System.

Appetite is good.

Does not like potatoes and milk.

Teeth. Complete and good.

Tongue is coated.

Vomited once after a bout of coughing.

Constipation has been present since last asthmatic attack.

Faeces. No tubercle bacilli present.

Abdomen. Nothing abnormal to note. Liver is just palpable at costal margin. Spleen is not palpable.

Test Meal..Total acidity = 12.

Free hydrochloric acid = 0

Much mucus present.

Bile absent.

Integumentary System.

Reaction of skin to stroking positive.

Skin test:- Swansdown +++

Milk. +

Delayed skin reactions to organisms of the Sputum - negative.

Von Pirquet's tuberculin test - negative.

Nervous System.

Higher cerebral and mental functions are normal.

Cranial nerves - normal.

Cervical sympathetic - cilio-spinal reflex is active.

Motor functions - normal.

Reflexes. Superficial are very brisk.

The plantar reflex gives an extensor response.

Deep - brisk.

Organic - normal.

Sensory functions appear normal.

Vasomotor and trophic functions are normal.

Locomotory System.

Bones, joints and muscles are normal.

Diagnosis.

Asthma:- Type 1. Childhood.

Treatment.

A The Attack.

If the child had not already had an emesis induced, this was done. Tickling the throat, giving quantities of sodium bicarbonate solution or salt and water were all tried; usually it was necessary to give Ipecacuanha Wine in doses of one teaspoonful.

Liquor adrenalin hydrochloride was given subcutaneously in a dose of 0.05 c.c.

The room was kept warmed and ventilated.

The back was rubbed with unguent capsicum.

First week after attack.

Ephedrine hydrochloride gr. ½ was given at night.

A mixture containing potassium iodide (grs.1), liquor arsenicalis (½ minim), tincture of atramonium (1½ minims) in syrup was given thrice daily.

Diet consisted of liquids and semi-solids. Milk was given in the form of Nestle's sweetened, because first, fresh cow's milk was refused, and secondly, because it served as an avenue for the exhibition of sugar.

Syrup of figs was given daily as an aperient.

Treatment of the fundamental cause.

This must be considered under the following:-

(a) avoidance of predisposing cause;

(b) avoidance of emotional stress;

(c) attention to diet and the giving of sugar and hydrochloric acid;

(d) alleviation of symptoms;

(e) dealing with sources of irritation;

(f) specific.

(a) Avoidance of Predisposing Causes.

Attacks of asthma followed the placing of the child in an outhouse. Careful investigation revealed the interesting fact that in this outhouse was stored, amongst other things, a lost of old swansdown. On skin testing with swansdown protein, a marked positive reaction was obtained.

All materials containing swansdown have accordingly been removed from the house.

The child has been excluded from contact with anyone suffering from "colds" as much as possible

(b) Avoidance of Emotional Stress.

The little patient was subject to a lot of "teasing" at home. This has been forbidden.

She was taken to hospital for the first fortnight of treatment. Here her whole condition rapidly improved. On her return home, she was put to sleep alone in a well-ventilated room. Kapok pillows and bedding were installed in her room.

(c) Attention to Diet.

No food of any kind was allowed after six o'clock in the evening. The patient did not relish milk, to which in fact she reacted by skin-testing with a positive result. To overcome this, specific desensitisation with milk was carried out, as described later.

Constipation was treated by the extra consumption of fluids and gentle abdominal massage.

Sugar. She was given a stick of barley-sugar at bedtime, and her mother was encouraged to give her as much as she asked for.

Hydrochloric Acid. This was given in doses of 30 minims, in a mixture with a grain of pepsin and 30 grains of pure dextrose, three times a day before meals, for a period of 3 months. It was then given every other week.

(d) Coryza was rigorously treated with alkaline nasal sprays during the day, and eucalyptol, menthol and chloretone sprays at night.

The cough disappeared following treatment of the nasopharynx and the improvement in her general health.

(e) Sources of Irritation.

Her tonsils were removed by guillotine and adenoids curetted. Thereafter her nose and throat were kept clean with Dobell's solution used as a spray. The mother was advised in the importance of getting the patient to breathe properly through her nose, and of giving her breathing exercises regularly and systematically.

(f) General Health.

Cod liver oil and malt was given regularly during the winter and spring, along with the syrup

of iodide of iron.

The child was confined to bed only in the presence of fever.

Tepid baths were ordered to be given, followed by a cold sponge, daily.

The mother was advised to keep the child in the open air as much as possible.

(g) Specific Treatment.

Desensitisation with milk was effected by giving very small quantities along with the pepsin and hydrochloric acid mixture. By gradually increasing the amount, it was eventually found possible to give the child milk in quantities. She, still however, did not care for it.

Progress Notes.

No illnesses have occurred since the above date of examination.

State on examination - October 1932.

The child now weighs 36 lbs.

There has been no cough nor other subjective phenomena.

The nasopharynx is healthy.

The chest expands one and a half inches.

The dullness of the manubrium sterni has practically disappeared.

The eosinophilia is still present.

She can now drink milk with no untoward effects.

The mother says the child has been, and is extremely well.

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CASE NO. 6.

Name:- Percy J.

Age:- 38 years.

Occupation:- Clerk.

Single.

Date of Examination:- September 1929.

Complaint:- Attacks of dyspnoea, occurring suddenly at night, accompanied by loud wheezing and tightness in the chest, and followed by a cough.

Duration of illness:- Sixteen years,

History. Personal.

In May 1916, whilst in the Army at Tidworth camp, he had what he thought was an ordinary "cold". During the night of the following day, he was suddenly awakened in the early hours of the morning by extreme shortness of breath and a feeling of suffocation. After a little while he began to wheeze. This lasted about an hour, during which time he struggled for his breath. Finally, a cough developed which was paroxysmal. At the end of one paroxysm he coughed up a little sputum, whereupon his symptoms eased off and he fell asleep. During a stay of three years in this camp, he had

odd attacks similar to the one described. These were attributed to contact with horses. In February 1919, he had influenzal pheumonia, from which he took a long time to recover. Since then on, he has had frequent attacks of asthma, and has hardly ever felt really comfortable about his chest. He seems always to have one or other symptom present.

(a) Factors influencing an attack.

His attacks are more frequent in the Winter and Spring.

He is always more comfortable at the seaside.

Contact with horses makes his symptoms much worse.

Milk does not seem to agree with him.

Offensive odours and north-easterly winds affect him adversely.

(b) Nature of the Attack.

Prodromata are well marked. They consist of:-

A fullness of the head;

Itching of the eyes; and

Running of the nose.

The attacks originally used to last two to three hours; now, he is really not free from symptoms for at least twenty-four hours.

The frequency is much greater than it was. There now are periods when he has attacks daily.

Relief is usually obtained from the hypodermic administration of evatmine, which he administers himself. Various powders - Potter's and Tucker's - once were useful to him; now they seem to suffocate him.

Coryza and wheezing are the two most prominent symptoms; his cough is, however, very troublesome and he expectorates a large amount of sputum.

Pains of an aching character are felt in the right side of his chest after much coughing.

(c) Health between attacks.

He never really feels well. Weakness and malaise are nearly always present; and dyspnoea inconveniences him very much. Cough is a persistent source of annoyance to him.

(d) Previous illnesses.

Past. Varicella when five years of age.
Measles when six years of age.
Submucous resection in 1914, because of nasal obstruction.

Present. Bronchitis.

(e) Other Allergy.

Past. Hay-fever.

Present. None.

History. Family.

Father - age 65 - alive and well.

Mother - age 65 - alive and well.

Brother - age 32 - alive and well.

Family history of allergy.

Antecedents.

Mother - migraine.

Father - asthma, hay-fever.

Contemporaries.

None.

History of Previous Treatment.

Evatmine)
) For the relief of attacks.
Potter's "asthma cure")

Vaccine therapy - autogenous - 1921.

Ultra-violet light therapy - 1926.

Symptomatic treatment of bronchitis.

External Particulars of Home.

His present home is built on a chalk and clay soil. It is low-lying and in an open locality. It is very quiet. There is a small garden. It is situated near a small dairy. The atmosphere is very clear and singularly clear from odours.

The locality is frequented by horse-riders.

There is no other known case of asthma in the locality.

Internal Particulars of Home.

The patient was born in his present home, and has lived there about thirty years.

It is dry, being heated by coal and wood fires. An oil-stove is sometimes used for heating odd rooms.

The floor is wood on cement.

Six rooms are used, which are crowded with furniture.

One plant - an aspidistra - is kept indoors.

It is lighted by oil lamps.

Window space is poor and ventilation the same. The windows are kept open day and night.

There is very little dust.

Washing and dusting are the methods of cleaning.

Carpets, linoleum and rugs are used.

All walls are papered, except the scullery which is distempered.

	Horsehair.	Feathers.	Flock.	Kapok.
Cushions	—	+ +	+	—
Bedding	+ +	+	+	—
Pillows	—	+ +	+	—
Upholstery	+	—	+	—

Feather eiderdowns are used.

All articles in patient's room were flock. He had, however, one feather pillow.

One dog is usually kept as a pet.

State of Examination.

He is sharp and above the average intelligence.

Height 5 feet 6 ins.

Weight 9 stone 2 lbs.

Development is normal.

Muscularity is poor.

In appearance, he is ever alert and watchful, nervous and anxious.

His attitude is rather a stoop.

No obvious morbid appearance is present.

His temperature is normal.

Respiratory System.

Subjective Phenomena.

Cough is a well marked symptom. There are two types in this patient, one which is nearly always present, and one which is the accompaniment of the termination of an asthmatic attack. The former is worse first thing in the morning and during damp foggy weather. It is accompanied by the expectoration of much sputum. The cough of the attack is definitely paroxysmal and seems to relieve the previous wheezing.

There has been no haemoptysis.

Dyspnoea. This is, of course, worse at the beginning of an attack. It is then obstructive in type and paroxysmal in nature. It, however, tends to occur in between attacks as well. It is easily brought on by exertion, and is inspiratory as

opposed to the expiratory type afore-mentioned.

Pain. Towards the end of an asthmatic attack the patient feels pain, aching in character, over the right side of the chest, which is not localised to any definite place.

Breathing. Costo-abdominal in type, the costal element predominating.

Eighteen breaths per minute.

Rhythm is regular.

Sputum. There is fair amount of greenish-yellow sputum, which appears to be getting more abundant. It contains eosinophils, Charcot-Leyden crystals, Curschmann's spirals, and abundant micro-organisms. The latter, on cultivation, are found to be micrococcus catarrhalis and a haemolytic streptococcus.

Tubercle bacilli have not been detected on repeated examination.

Naso-pharynx. The nose is straight and narrow. The nasal septum has a perforation - a third of an inch in diameter - at its anterior end. The mucous-membrane over the turbinates is pale and oedematous looking. The frontal sinus is opaque to transillumination on the left side.

The pharynx is congested with muco-purulent discharge from the posterior nares. It is studded with granulations, and congested.

The tonsils are buried and difficult to see. He never has had tonsillitis.

Thorax.

Inspection.

The chest is funnel-shaped. The left shoulder appears flattened. The upper chest seems distended.

Measurements:-

Anteroposterior	9 inches.
Transverse	11 inches.
Circumference	34½ inches.
Thoracic Index	82
Expansion	1 inch.
Subcostal Angle	70°

Sigson's furrow is well marked.

Litten's diaphragmatic sign is absent.

Movements are limited, yet appear forced, and mostly take place in the upper part of the chest. The costal borders converge on inspiration.

Palpation.

This confirms inspection as to form and movement.

Vocal fremitus is decreased generally.

It is more pronounced over the right apex than over the left, and over the left infraclavicular region than over the right.

Percussion.

Kronig's isthmus measures at narrowest point:-

right - 1¼ inches.

left - 1½ inches.

The percussion note is loud and drumlike. The pitch is lower than normal. Hyper-resonance is general.

Posteriorly, resonance extends to the level of the tenth thoracic spine on the left side and to the level of the eleventh on the right.

Tidal percussion is:-

right - 1½ inches.

left - 1 inch.

The variation in the costophrenic sinus constitutes Williams' sign, and in this patient it is suggestive of a lesion at the left apex.

Auscultation.

Breath sounds are generally feeble and indistinct. They are best heard in the supraclavicular fossae where they are bronchovesicular.

Râles are present posteriorly - inspiratory and expiratory. They are unaffected by coughing. They obscure the breath sounds, and are sonorous and sibilant in type.

Bronchophony is present over the sternum and interscapular region.

D'Espine's sign is positive.

X-rays.

This shows a peak on the left side of the diaphragm suggesting an adhesion. The excursion of this muscle is good on the right side but not so extensive on the left.

Hilum shadows are extensive.

The lung fields are clear yet mottled, resembling tubercular infiltration.

Clinical condition during an attack.

The chest looks full and fixed. In spite of active muscular efforts there is very little expansion. The breathing is costal, the diaphragm is low and movement is much restricted. Inspiration is short, expiration much prolonged, laboured and accompanied by wheezing râles. Percussion is hyper-resonant, and amounts to Biermer's "box-tone". The cardiac dullness is obliterated and the liver dullness very low. Sibilant and sonorous râles obscure the feeble breath sounds.

Haemopoietic System.

There are no subjective phenomena.

No glands are palpable.

Blood.

Size of red blood corpuscles	7μ
Haemoglobin	95%
Red blood corpuscles	6,040,000
White blood corpuscles	13,120
Colour Index	0.8.

Differential Count.

Polymorpho-nuclears	55%
Small lymphocytes	27.5%
Large mononuclears	6.75%
Eosinophils	10%
Basophils	0.75%

Arneth Count.

Type 1	1%
Type 2	12%
Type 3	38.5%
Type 4	37.5%
Type 5	11%

Wassermann - negative.

Van den Bergh - indirect reaction.

Blood bilirubin - 0.5 mgm. per cent.

Blood calcium - 10 mgm. per cent.

Blood sugar - 50 mgm. per cent.

Circulatory System.

No subjective phenomena.

Pulse. Arterial wall is not palpable.

Frequency - 70

Rhythm is regular.

The wave is normal in character.

Blood pressure:- systolic 130

diastolic 78

Heart

No pulsations visible.

Apex-beat palpable in the sixth inter space, 21 inches from mid-sternum.

Borders $\frac{\overline{111}}{\frac{1}{2}/2\frac{1}{2}}$

There are no murmurs.

There is an accentuation of the second sound in the pulmonary area.

X-rays.

Show a long and narrow heart shadow. The aortic shadow is normal. The posterior cardiac space is clear.

Urinary System.

No subjective phenomena.

Urine.

Lemon-coloured and clear.

Two and three quarter pints passed in twenty-four hours; proportion of day urine to night urine 4:1.

Specific gravity - 1,005.

Acid reaction, Ph 6.

Urea excreted on standard diet - 2%

No abnormal constituents.

Deposit - mucus.

Paroxysmal urine.

Reaction acid - Ph 6.5

Specific gravity, 1,024.

Ether reaction present.

Urates present.

Chlorides decreased.

Smell of ammonia pronounced.

Alimentary System.

Appetite is not good.

Distension present after meals.

Gastric flatulence occurs after food.

Lips are dry.

Teeth. Those present are good.

There are no upper molars and premolars.

Gums are healthy.

Tongue is coated.

Fauces - anterior pillars are reddened.

No vomiting has occurred.

Constipation is not present.

Faeces. No occult blood present.

Tubercle bacilli not found.

Abdomen - nothing to note.

Test Meal. Total acidity - 25.

Free hydrochloric acid - 0.03%

Laevulose tolerance test.

Blood sugar rose to 0.15 per cent and did not fall to normal with the two hours.

Integumentary System.

Reaction of skin to stroking is strongly positive.

Skin tests.

Horsehair + + +
Cow hair + + + Very strong positive.
Dog hair +

Delayed skin tests to micro-organisms of sputum - positive.

Von Pirquet's tuberculin test - negative.

Reproductive System.

Nothing to note.

Central Nervous System.

Higher cerebral and mental functions.

In intelligence he is above the average. He is very keen and critical during examination, and very eager to learn his condition.

He is decidedly emotional and easily impressed.

He states that sleep is disturbed by his asthmatic attacks.

Memory is very good.

Cranial Nerves.

His sense of smell is diminished.

Glasses are worn for astigmatism.

Cervical Sympathetic.

Cilio-spinal reflex is very active.

Flushing of face and neck occurs during examination.

Motor functions.

He is quick in all his movements.

Reflexes.

Superficial - very active.

Deep - very active.

Organic - normal.

Sensory functions.

Headache is complained of, said to be due to worry over his condition.

Vasomotor and Trophic functions.

Normal.

Cerebro-spinal fluid.

Clear and colourless.

Protein - 0.02%

Sugar - 0.05%

Chlorides - 0.75%

Cells - 3 lymphocytes per c.mm.

Pressure - 1 drop per second.

Locomotory System.

Nothing abnormal.

Diagnosis.

Asthma.

Type (2) Adults.

Subtype (b)

Treatment.

The Attack.

The hypodermic injection of 0.5. c.c. evatmine.

Room made warm, quiet and airy.

Brandy - ℥ss - in black coffee given.

Back rubbed with unguent capsicum.

Hot-water bottles applied to feet.

First week after attack.

Ephedrine hydrochloride gr.½ at bedtime.

Potassium iodide, gr. 10 given thrice daily.

Magnesium sulphate - ℥ss - given each morning.

Blood therapy.

5 c.c. blood withdrawn from the arm and immediately injected into the buttock, twice during the week at equal intervals.

Diet.

Glucose - ℥i - given night and morning, in a little water, on an empty stomach.

Brandy - ℥ss - given each night.

First two days - fluid and semi-solid diet; thereafter only easily assimilated foods given, and

vegetables only as purées.

Treatment of Fundamental Cause.

This will be considered under the following sections as outlined in previous cases.

(a) Avoidance of predisposing and exciting causes.

The history brings out the presence of hypersensitiveness to horsehair. This is confirmed by the skin tests. The latter also discloses hypersensitiveness to cowhair and even dog hair. And so, in spite of specific desensitisation which has been carried out, it is necessary to avoid contact, whenever possible, with horses, cows and dogs. In view of the proximity of a dairy and the popularity of the neighbourhood for riding, this has not been easy. Specific desensitisation has been of great service, including the effect produced on the mental condition of the patient.

Cycling and walking against winds has been forbidden; and he has been advised to avoid driving in open cars.

A winter holiday in the south-west of England has been recommended, instead of the usual summer one.

He was advised to try and obtain work at the seaside. This he did at Bournemouth, where he

was very much better. Unfortunately, he developed an attack there, which he maintains was brought on by the worry of being away from home.

The milk in his diet has been curtailed. Condensed milk has been substituted where possible.

Although very difficult to carry out, he has made great efforts to avoid contact with persons suffering from "colds". He has been monthly, during winter and spring, vaccinated prophylactically with Burroughs and Wellcome anticoryza vaccine No. 4. The first two of these injections have to be 0.1 c.c. and 0.25 c.c. as the tendency is for an asthmatic attack to result.

(b) Avoidance of fatigue, overwork and emotional stress.

This patient is obviously allergic, and there is no doubt that physical stimuli have produced attacks of asthma in him. Living at home, as he is, this has been explained to his family. Moreover, the process has been explained to the patient himself. Indeed, treatment by psycho-analysis for an hour every week for six to eight weeks was carried out with very satisfactory results.

The expectation of an attack, undoubtedly predisposed him to some nocturnal attacks. Many

of these attacks, to all intents and purposes really asthmatic, were definitely relieved by hypodermic injections of sterile distilled water, care being taken of course to prevent the patient seeing what kind of injection was taken up into the syringe.

With the above in view, it is obvious how necessary it is to avoid emotional stress of any kind.

Fatigue and overwork must, of course, be prevented. At the same time, much evil had been done in this patient by having him to believe he was a chronic invalid. This began when he was invalided out of the Army with asthma and was granted a pension because of it. The obvious psychological factor which he has confessed to me, is his fear of losing his pension. He has, after much persuasion, been working regularly in the garden and doing a lot of walking. It has been pointed out to him the seriousness of doing nothing at all. Provided he does not get over-fatigued, the necessity of some occupation has been stressed.

(c) Attention to Diet.

There are two important items to note in this section. The more so of the two is the presence of definite hypochlorhydria; and the second is

the absence of some very important teeth.

Dilute hydrochloric acid has been given as a beverage during meals in doses of a drachm thrice daily in orange juice.

The long absence of the essential teeth of the upper jaw led to much difficulty in the fitting of a comfortable and appropriate upper denture, which was, however, eventually achieved.

The attention to these two details has resulted in loss of the flatulent dyspepsia, improvement in appetite, increase in weight and much sounder sleep. They have, no doubt, also contributed to the alleviation of his asthma.

Small, easily digested meals have been adhered to, the principal meal being at noon and only a light supper partaken of.

Moreover, this patient, with a low blood sugar and definite evidence of liver damage, was clearly likely to benefit from the administration of glucose. This was given in doses of an ounce, in water, morning and evening, on an empty stomach.

(d) Alleviation of symptoms.

Cough. The paroxysmal cough was best relieved with a linctus, such as oxymel of scillae, syrup of

tolu and the compound tincture of camphor, twenty minims of each.

The early morning cough was satisfactorily treated with a saline, sodium chloride gr. 3 with sodium bicarbonate gr. 10 in spirits of chloroform and water.

For the bronchitis, ammonium chloride was prescribed and given for periods of seven to ten days at a time. This also helped to combat the tendency to alkalosis and thus to ward off attacks. By its interrupted use, the liability to upset the digestion was averted.

Headaches. Bromides and aspirin were prescribed when necessary. It is interesting to state that this patient has been in the habit of taking aspirin to abort his attacks.

The treatment of the alimentary symptoms has already.been discussed.

(e) Dealing with sources of irritation.

There was excessive muco-purulent secretion from the naso-pharynx. Accordingly, treatment with the Dowling pack was carried out. Long, thin rolls of cotton wool, impregnated with ten per cent argyrol solution, were packed into all possible recesses, left in position for half- an - hour and

then removed. This was done twice a week for three weeks. A week later, naso-pharyngeal tretment was carried a stage further. Inhalation of small amounts of carbon dioxide for five to ten minutes each morning, through tubing into each nostril, was carried out. This was done for a fortnight. Thereafter the patient was instructed to spray nose and throat every morning with Dobell's solution.

This treatment resulted in great improvement of the naso-pharynx and the loss of the catarrhal condition.

(f) Vaccine Therapy.

An autogenous vaccine prepared from the organisms of the sputum and smears of the nose and throat, to which the delayed skin tests were positive, was administered. It consisted of micrococcus catarrhalis and a haemolytic streptococcus. The dosage ranged from five to a thousand million, given in weekly doses. There was a mild reaction to each dose.

(g) Treatment of complications.

Hypertrophic emphysema and enlarged mediastinal glands are the two complications encountered.

For the former, the exercises, recommended by Hurst (140) and employed at Guy's Hospital, were carried out systematically. Each of such exercises begins with expiration and ends with expiration, the object being to reduce the size of the thorax. Each part of an exercise is performed three times, so that there are four expirations to three inspirations in each part, followed by a short pause at the end of each inspiration and at the end of each part. Inspiration and expiration are both performed through the nose.

By persevering with this treatment of remedial exercises, chest expansion was increased from one inch at the beginning to two and a half inches, at the end of six months.

For the enlarged mediastinal glands, life in the open as much as possible, cod liver oil and the syrup of iodide of iron were prescribed.

(h) General Health.

This has, to a large extent, been dealt with in the preceding paragraphs. There are, however, a few more important details.

First, it is unnecessary and unwise to confine to bed a patient of this type, except in the presence of fever. So this was avoided.

Secondly, he was made to sleep along in a well-ventilated room. No upholstered furniture was permitted in his room, and the floor was covered with linoleum - all this to avoid dust. Kapok was used for bedding and cushions.

Thirdly, a daily warm bath followed by a cold sponge and brisk rubbing with a rough towel was ordered.

(i) Specific treatment.

Auto-haemo-therapy, beginning with 4 c.c. and increasing by 1 c.c. each time to a maximum of 10 c.c. was done weekly for six months.

Desensitisation to a mixture of animal hairs was also undertaken. Beginning with a 1 in 100,000 dilution, this was a prolonged measure. Eventually, the patient was able to stand 1 c.c. of the stock solution. Skin-tests with this solution were negative at the end of the treatment.

Progress Notes.

July 1930 - Asthma.

State on examination - October 1932.

There have been no further definite attacks of asthma since July 1930. He has, however, complained at odd times of thoracic discomfort, of short duration.

His weight is now 10 stone 6 lbs., and remains steady.

His muscles are no longer atonic, but firm and developed.

His naso-pharynx is healthy; but, of course the perforation is still present. He still is subject at times to "nose running".

His chest expansion is now three inches. The whole chest moves well.

Eosinophilia is still present.

He no longer suffers from indigestion.

Skin-tests to animal hairs are now negative.

His mental condition is very much improved.

His general health is very good.

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Summary.

Introduction.

Asthma is the term used to designate a symptom-complex, which is more than mere bronchospasm. It definitely embodies a syndrome with certain absolute characteristics. It is merely one of a group of diseases, which are fundamentally the same in origin; in which, however, the manifestations vary according to the part of the body involved. In asthma, this is the bronchial tree.

The basis of the whole subject is Hypersensitiveness, a state in which abnormal reactions to some foreign agent occur. In the laboratory animal, this state is termed Anaphylaxis; and in the human being, it is designated Allergy. It may follow the inhalation or ingestion of, or injection or skin contact with the specific irritating substance. The antigen is not necessarily protein in nature. The Prausnitz-Kustner reaction clearly shows that it circulates in the blood.

Asthma represents the lung manifestations of allergy. The expression of this state of allergy necessitates, however, the presence of an exciting cause and of a predisposition, associated, it may be, with vagotonia.

The history of asthma discloses the interesting fact that the syndrome has been recognised from earliest times. Present-day knowledge is the outcome of strenuous and pains-taking investigations. One by one the various factors concerned have been brought to light. First, there came the establishment of hereditary influences. Then followed in due course the link with anaphylaxis, the sphere of skin-testing, the prominence of the nervous factor, the question of nasal pathology, the use of adrenalin, the action of histamine, and the existence of allied conditions.

General Etiology.

A milestone in the elucidation of the problems of asthma and allied diseases was the recognition of anaphylaxis as a condition occurring in laboratory animals, with definite symptoms and a definite pathology, and having

well-marked characteristics. The essence of this condition has been shown to be dependent upon the distribution of the non-striated musculature in the various species of animals. In an animal dying from anaphylactic shock, the chief pathological condition is a contraction of the smooth musculature of the bronchioles, resulting in an inflated condition of the lungs. This condition closely resembles that found in the lungs of a human being, suffering from asthma. It is not universally accepted, however, that anaphylaxis as such ever occurs in man. Accordingly, a new term, Allergy, was introduced to designate this state of altered reactivity occurring in human beings. This hypersensitive state is also characterised by certain definite details. A comparison of the salient features of Anaphylaxis and Allergy renders obvious the fact that whereas these two conditions are related fundamentally they are not one and the same in detail. Moreover, Allergy is not just merely a state of altered reactivity to varied substances. There are important modifying or predisposing non-specific factors concerned. It is suggested

that there exists in susceptible subjects a balanced allergic state. Should such non-specific factor be disturbing this balance when the specific allergen intervenes, then allergic symptoms will ensue.

The causation of the bronchial obstruction in asthma has been the subject of much investigation. Anatomical, physiological and experimental observations uphold the view that this obstruction is due to a spasm of the bronchial musculature. At the same time, the importance of reflex vagal stimulation cannot be overlooked, especially as it seems possible that the vagus may be rendered more irritable than normal by the circulation of foreign protein. Indeed, it is probable that in allergic conditions a very important role is played by the vagus.

In a normal individual there is preserved between the two component parts of the involuntary nervous system a balance. It is suggested that in allergic diseases this balance, also, is upset with a consequent predominance of the parasympathetic or vagal element. In support of this are the facts that broncho-spasm is the classical example of vagal stimulation in man

and that invariable relief of an asthmatic paroxysm follows the hypodermic administration of adrenalin, which stimulates the sympathetic. Further, it is possible that an abnormal blood chemistry may be responsible for the vagotonia. At any rate, it is known that the sensibility of the vagus is increased by the presence of foreign protein.

The functional activity of the autonomic nervous system is closely associated with the endocrine glands. Cases of allergy are often complicated by endocrine disorders, the thyroid being most often involved. It is important to establish to what extent the allergic condition of the patient is due to the glandular dysfunction. The determination of the basal metabolic rate is of great value for this purpose. The involvement of the suprarenal is rather more pertinent. Whereas there can be no doubt that suprarenal inadequacy in itself cannot be altogether responsible for the allergic state, there are certain facts which support the view that intermittent dysfunction of this gland may be present and lead to a relative vagotonia. These are the remarkable effect of adrenalin in

relieving the asthmatic paroxysm, the effect of fatigue in predisposing to such an attack, and the biochemical make-up of the allergic individual. That the sex glands may also be involved in allergic conditions is definitely brought out by clinical data. There must be a disturbance of the normal balance of the internal secretions, which is enough to stimulate the vagus. At any rate, allergic patients in general do not fall into any picture simulating increased or decreased endocrine dysfunction.

Nasal pathology has for long been linked up with the etiology of asthma. The basis of this nasal factor is the so called "ethmoid region" an area of the nose, stimulation of which leads to bronchospasm.. An anatomical consideration of this area shows how difficult it is to obtain complete eradication of any chronic infection. The majority of present-day observers favour the idea that the clinical lesions found in the sinuses, together with the polypi in the nose, are merely a part of the fundamental pathological changes which occur in asthma. The lesions in the nose are so common in this disease as to be almost a clinical characteristic and they may be of diagnostic importance.

At a time when so many diseases are being attributed to toxaemia, it is not surprising that asthma should be included in the list. There can be no question that in the nose a focus of infection very often does exist. Its place in the etiology has been duly considered. There remains as a source the much blamed alimentary tract, with the inevitable intestinal toxaemia. It is well known that vomiting and defaecation may relieve an asthmatic paroxysm; but such events must occur reflexly in an individual who has inherited the predisposition to manifest these allergic responses. On the other hand, some "toxic" substance does appear to be generally distributed in allergic individuals. Biochemical evidence of liver inefficiency and the discovery of proteose in the urine uphold such a theory.

A subject of much practical importance is the existence of allergic reactions, arising from the ingestion of wholesome and normally well-tolerated foods. Such symptoms of food allergy are especially frequent in children. Their importance lies in the fact that the condition to which they give rise may be mistaken for a surgical emergency.

Syphilis has no place in the etiology of asthma. It is, however, a popular idea that asthma is a manifestation of tuberculosis. This is unfortunate, as tuberculosis merely predisposes to asthma in the same way as any other respiratory infection, by virtue of the tissue damage which results. The proteins of the tubercle bacillus are incapable of producing allergic manifestations, such as asthma; but the secondary bacillary invaders of tuberculous cavities are a very important consideration.

Clinical conditions seem to be of foremost importance in any theory of "tissue damage" and its relation to allergic phenomena. For many such phenomena can be explained by this theory.

Asthma has for long been regarded as being of nervous origin. Emotions such as grief and worry are predisposing factors upon which the allergic state develops; and expectation is perhaps the most common psychological factor. Granted that asthmatic attacks do occur without the intervention of any specific allergen, it is certain that they will not occur in persons who are not already allergic. The age-incidence

and the sex-incidence of the psychoneuroses and asthma are quite different. On the other hand, it is possible to conceive that a balanced allergic state may become upset by exhausting and depressing mental states, exposing the body to the action of allergens. A decrease in the normal secretion of adrenalin, with a disturbance of the vago-sympathetic balance,may be the solution of the problem.

The behaviour of allergic diseases to locality and environment is capricious in the extreme. It is impossible to foretell what will suit any individual patient best. With regard to altitude, it is at least refreshing to realise that nearly all asthmatics lose their symptoms at a height of over four thousand feet. It seems difficult to escape from the conclusion that the biochemistry of the blood is the responsible factor. The influence of house dust in the causation of asthma has been very carefully investigated; and excellent results have been obtained in suitable cases by the use of dust-free contrivances.

There is an urgent need for the establishment of convalescent homes in suitable situations, where incidentally suitable treatment can be

carried out, for chronic refractory asthmatic children. The neglect of such patients, under the present difficulty economic conditions, endows the State with the upkeep of many a pitiable individual with a deformed chest and pulmonary over-distension, incapbale of doing any work whatsoever.

In the consideration of benefits derived from spa treatment, there must be taken into account the effects of routine and psychology. At the same time, there is evidence to show that the presence of free carbon dioxide in the vapours at these establishments is of definite value in many cases of asthma.

Asthma and Allergy.

The relation between the symptoms of asthma and the causative agent may be clear-cut or obscure. And the causative agent may be extrinsic, such as an animal or plant emanation, or intrinsic, when it arises within the body, in the nature of an infection. Whatever the cause, the individual is hypersensitive to a substance of varying chemical nature. Such an individual can be shown to possess certain very definite

characteristics. These are a personal history of other allergic conditions, a family history of allergic manifestations, an ability of the skin to react positively to foreign substances, a blood eosinophilia and a dramatic response to adrenalin.

Asthma may be classified (a) according to etiology, and (b) according to pathology, but neither classification is altogether satisfactory. In the former, extrinsic asthma refers to patients whose symptoms are due to an extrinsic cause, such as animal emanations; and intrinsic asthma includes those whose symptoms are due to bacteria and reflex causes. Bacteria may give rise to asthma in three ways. First, there may be a direct sensitiveness to some bacterial product. Secondly, a combination of exposure to the specific allergen and bacterial infection at one and the same time may lead to the production of asthmatic symptoms, whereas no such symptoms may arise on exposure to these two elements independently. Thirdly, bacteria may prolong and intensify an attack of asthma which has started from any cause.

In the group composing the reflex cases, an interesting type is described - the gall

bladder type - in which gall-stones and gall-bladder disease are but rarely found. Many theories have been advanced to explain cardiac asthma, which seems in fact to be due to a reflex effect from aortic irritation. The classification based on pathology fails because the opportunity to check the clinical conception by an autopsy is rare and because the various types tend to merge into each other.

There are six fundamental facts of Anaphylaxis, which are of great importance in the study of human hypersensitiveness. These are:-

(1) the fact that sensitisation to any foreign protein substance can be effected;

(2) the presence of an incubation period;

(3) the second dose of the substance concerned produces a reaction which is highly specific; and the Dale reaction;

(4) passive anaphylaxis;

(5) desensitisation; and

(6) the Arthus phenomenon.

There are two theories as to the site of the anaphylactic reaction, the humoral and the cellular. The six facts enumerated above support one or other. It may be thus concluded that the principal reaction in anaphylaxis takes place in the cells or on their surface.

The diversity of the symptoms of anaphylaxis in different animals depends primarily upon the distribution of the non-striated musculature. The mode of sensitisation is not the same in man as it is in animals. In man, hypersensitiveness develops gradually, and is not usually restricted to one particular substance. Moreover, desensitisation is definite in anaphylaxis but less defined in human hypersensitiveness.

The typical experiment of anaphylaxis in animals can only be produced with proteins. Much importance is being attributed to the carbohydrate constituents of proteins. So far, however, the chemistry of anaphylaxis is unknown in its essentials, though it evidently depends upon complex protein substances. The fact that the symptoms of anaphylactic shock are the same by whatever produced, suggests the formation of a poisonous principle which is the same in

each case. The various researches to try and discover such a substance have given rise to a number of theories regarding anaphylactic shock. Of these, two are worthy of consideration - the Proteolytic and the Histamine. In support of the former are the facts that animals can be partially desensitised by treatment with peptone and that peptone shock causes a loss of coagulability of the blood, thus resembling anaphylactic shock. Histamine produces a condition more like traumatic shock, with vaso-motor paralysis; and its action further differs from true anaphylaxis in that it is still able to produce a strong reaction in the uterus even though this has been desensitised by treatment with specific serum.

Whereas in the experimental animal anti-bodies or ferments are necessary for the splitting of the proteins to enable them to be absorbed by the cell, man can become sensitive to substances which do not require this antibody reaction.

The nature of the particular chemical complex concerned in the elicitation of a positive skin test and in desensitisation has

not been precisely defined. One of the structural units is apparently of carbohydrate nature, which has been demonstrated in horse serum and in bacterial extracts.

The chemical problems of experimental anaphylaxis and human hypersensitiveness are obviously very similar.

Mode of Desensitisation.

Proteins are substances of complex nature which require the formation of antibodies before they can be dealt with by the cell, and they are therefore antigens. These antibodies are first formed in the cell itself - cellular antibodies - and later appear in the surrounding medium - circulating antibodies. The presence of the latter can be demonstrated by the precipitin reaction and the fact that blood, artificially sensitised with horse serum, can transfer the sensitive state to a normal animal. These antibodies do not persist indefinitely; and the state of passive sensitisation in the recipient normal animal must depend upon their length of existence. The failure to demonstrate circulating antibodies in asthma and hay-fever patients may be because the resistance of the individual has not been strong enough to bring

out reacting bodies in such quantities as to be recognisable in the circulating blood. The Prausnitz-Kustner reaction is also of value in this connection; there appears to be some substance in the sera, other than precipitins, responsible for the transfer of sensitivity; the word "reagin" is used to designate this substance. Reagins and skin tests go hand in hand; and they may persist indefinitely in the circulating blood, though this is queried. The existence of cellular antibodies is proved by the Dale reaction and by Manwaring's transfusion experiment. Moreover skin tests must depend on their presence. In conclusion, it may be said that cellular and circulating bodies are important in all forms of anaphylaxis and allergy; and other probably related antibodies, reagins, persist as evidence of the original sensitising process.

Desensitisation.

This phenomena may be explained in three ways. First, it may be due to the antibodies becoming so saturated with the sensitising protein that they can no longer unite with any more doses of the same protein. Secondly, it

may be because the antibodies and antigens are prevented from uniting by some unknown factor. Thirdly, it may be a condition which is the result of the prevention of the reaction toward the hypothetical toxic substance caused by the antigen-antibody reaction. In man, clinical observation would seem to support the first of these theories. The failure to find that desensitisation has occurred after recovery from a general reaction in a hypersensitive patient makes it difficult to see how desensitisation occurs in any ordinary sense in human allergy.

Bacterial Allergy.

Whereas the same manifestations which result from the entry from without of foreign protein substances into the body can be produced by causes within the body, it does not seem possible that the mechanism is the same in each case, for two reasons, chiefly. The foremost of these is the completely different behaviour of the skin test. The other is the treatment with vaccines very rarely results in the production of a general reaction. Indeed, in bacterial

allergy, there appear to be two types of reaction. The first is akin to protein anaphylaxis, and the second is peculiar to bacterial hypersensitiveness. The essential part of this peculiar reaction is that it must involve injury to the tissues of the animal to produce pathological lesions of definite extent. So that the carbohydrate substance merely determines the specificity of the immediate anaphylactic or allergic reaction and has no antigenic properties; whereas the delayed inflammatory reaction of the skin test is obtained from whole bacteria or their nucleo-protein fraction. These delayed inflammatory skin tests obtained with bacteria and their products represent the remains of active infections that have past. Many asthmatic patients seem to be sensitised by a substance of bacterial origin, arising from some focus of active disease.

In desensitisation in bacterial allergy, the production of local reactions to therapeutic doses seems essential. In such circumstances, the question of the effects of histamine must obviously arise.

An interesting observation is that non-bacterial allergy may be expressed as a para-sympathetic or vagus syndrome, and that bacterial allergy may be expressed as one of the sympathetic system.

Spasmodic bronchial asthma and anaphylaxis.

There is substantial evidence to uphold the idea that spasmodic bronchial asthma is a manifestation of a condition like anaphylaxis in a sensitive subject. First, there is the similarity of the symptoms; next, the condition of the lungs at autopsy closely resembles that found in experimental anaphylaxis; and physiology has demonstrated that in anaphylaxis the bronchi are constricted from contraction of the bronchial muscles, and that this contraction is due to a direct stimulation of these muscles.

It is not universally accepted that anaphylaxis, as produced in animals, can be demonstrated in man. Such a condition has been described; it must, however, be exceedingly rare, as serumis now used so widely therapeutically. Serum disease is certainly not uncommonly encountered; but the true anaphylactic state, with its spastic contraction of the bronchial

muscles and its capillary disturbance, is certainly a condition of the rarest occurrence.

Though the mode of sensitisation varies somewhat in anaphylaxis and bronchial asthma, the resulting condition of hypersensitiveness is essentially the same.

Spastic contraction of the bronchial muscles and capillary disturbance are two pronounced features of vagotonia. Indeed, vagotonic patients show many of the characteristics of asthmatic subjects.

The Biochemistry of the amino-acids.

The amino-acids are all amphoteric, reacting as bases with acids and as acids with bases. Moreover, they ionize very slightly in solution in two ways. The majority of them are laevo-rotatory. They are variously derived from proteins. They unite amongst themselves to form di-peptides. The importance of these synthetic polypeptides lies in their similarity to the proteins, and their partially broken down products, the proteoses and peptones. When hydrolysed, polypeptides break down to amino-acids.

The pepsin of the gastric juice acts immediately on proteins to break them down to proteoses and peptones, setting free in the process at least twenty per cent. of the amino-groups.

In the intestines, bacteria attack protein decomposition products; and phenols, amines (including histamine) and acids are thus formed. These products are all absorbable through the intestinal wall. The liver is responsible for rendering innocuous such compounds when absorbed. If, however, the toxic compounds are produced in concentration greater than the liver can cope with, they may produce their pharmacological effects.

Recent observations tend to show that the chemical action of any bacterium depends in great measure on the medium in which it exists, and that, provided this medium contains a sufficient proportion of carbohydrate, products of the action are non-toxic.

Metabolism of Proteins in the body.

The gastric juice converts proteins through various stages into peptones. In the duodenum polypeptides and, perhaps, some amino-acids are

formed. The final breakdown into amino-acids occurs partly in the lumen and partly in the wall of the small intestine. Nucleosides are correspondingly the end-products of nucleo-protein metabolism. On absorption, the amino-acids pass to the liver, whence some proceed to the tissues to make up for wear and tear, and others undergo deamination. Finally, they are converted into glucose or yield acetone bodies or help to form bile-salts. There are, however, two which yield neither sugar nor acetone bodies; these are histidine and tryptophane, which are nevertheless essential for health and growth.

It is believed that the amino-acids resulting from protein digestion can stimulate cellular activity.

The end-products of protein metabolism are to be found in the urine. The urea of the urine is an index of protein intake, and also in starvation. Half the uric acid excreted in the urine is also derived from the nitrogenous intake, the other half being the result of tissue activity.

The end-products of tryptophane and tyrosine are excreted in the urine as ethereal sulphates,

The protein in the diet is thus the sole source of the nitrogen and sulphur which are needed for tissue repair. And it gives rise to the amino-acids, which go to form essential secretions and enzymes, Moreover, protein stimulates body metabolism and is a source of energy.

Relation of Proteins to Asthma.

The manifestations of allergy must be produced by the action of some poisonous substance of a characteristic and particular nature, formed when allergens come into contact with cells which bear their specific antibodies.

The injection into animals of such substances as peptone and histamine results in the production of symptoms resembling anaphylaxis. Now histamine is only one of a number of amines derived from protein metabolism. Such amines comprise two big groups, monamines and diamines. It is probable that the former, as well as the latter can, act as poisons to produce symptoms simulating anaphylaxis. Histamine is derived

from histidine, which is found in all the body tissues. On intravenous injection into animals it causes a contraction of smooth muscle and a striking fall in blood pressure. In man, the injection also causes a fall in blood pressure, but the effect is more transitory. When applied to the skin, characteristic wheal formation occurs. Histamine can be extracted from the mucous membrane of the intestine; and it can be produced by bacterial action. It is, in fact, of widespread occurrence. Now, injuries and wounds appear to liberate an intracellular substance, called "H-substance", which gives rise to shock and symptoms very similar to those produced by histamine. In cases of allergy due to cold, histamine-like reactions have also been described. Moreover, a proteose substance has been isolated from the urine.

The union of antigen and antibody in anaphylaxis and allergy seems therefore to injure the issues and thus liberate a histamine-like substance, which gives rise to symptoms. And the state of allergy seems characterised by a diminished resistance to histamine-like substances.

Protein skin reactions.

The object of a skin test is to demonstrate that the patient reacts to some foreign substance in a way different from normal individuals. It is based on the fact that those substances, which, when taken into the body by other routes than by the skin, are capable of producing allergic responses, will result in the formation of an urticarial wheal when brought into contact with the lower layers of the epidermis. Skin tests are also of value in demonstrating the activity of a known specific allergen. The allergens used in skin testing are mostly protein in nature.

The mechanism of a skin reaction is two-fold - the local formation of a substance of histamine-like nature, and a nervous reflex. Any reaction is entirely specific to the allergen concerned.

The relief of symptoms following the removal of a suspected allergen in the case of a positive reaction is definite proof of the value of such a reaction.

As sensitivity is most often concerned with environment and diet, tests should first be made concerning these two factors. The

time of year at which the asthmatic attacks occur is also a guide as to what should be tested for. It is important that steps should be taken to standardise the extracts and allergens in use, which unfortunately has not yet been done. The allergens used in skin-testing consist of inhalants, ingestants, infectants and injectants. These are put up in various ways. The tests may be performed through the skin or through mucous membranes. There are three modifications of the skin test - the cutaneous, the intradermal and the patch. In the cutaneous test the reaction reaches its height in about fifteen minutes and consists of an urticarial wheal with pseudopodia, surrounded by a pink areola. The number of positive reactions obtained is greater with the intradermal test. The patch test is used chiefly to determine susceptibility to external irritants, especially those of non-protein nature. Tests performed through mucous membranes - such as the conjunctiva - are most often used in the determination of pollen sensitiveness.

These skin reactions vary widely. The irritability of the skin to which they are due may change from time to time in the same individual.

The proof of the test is the effect produced by removal of the offending allergen, as to whether relief or not from symptoms is obtained.

Severe allergic reactions sometimes follow these tests. Various factors definitely influence positive results.

The methods of performing these tests all have their uses. These is little to be said as to their relative merits.

When using bacteria for these tests, the local reaction appears as a local inflammation and is delayed for twenty-four hours. An immediate wheal, such as obtained with other allergens, would suggest sensitivity to an existing infection. The delayed inflammatory reaction is obtained with whole bacteria or their nucleo-protein part.

Where the usual skin tests are impracticable, the use of the Prausnitz-Kustner reaction may be exceedingly helpful.

The accuracy of skin tests must of necessity vary with the substances used. With pollen and animal epithelia, they are very accurate.

A positive skin reaction indicates a definite, latent or specific sensitivity; a negative reaction denotes either a true absence of sensitivity or a pre-sensitisation stage.

Biochemistry of Asthma.

This shows the following characteristics:-

1. a low blood sugar;
2. a low cell chloride content;
3. a high amino-acid content of the blood;
4. a normal blood cholesterol;
5. a normal blood calcium;
6. a slightly lower figure than normal for blood phosphorus;
7. during the attack a complex nitrogenous substance of a proteose nature, the specific allergen, is secreted in the urine;
8. during the attack, the urine shows:-
   (a) increased free acidity;
   (b) increased specific gravity;
   (c) deposition of urates;
   (d) retention of chlorides;
   (e) increased ammonia excretion;
9. gastric analyses show a tendency to deficiency of gastric secretion;

10. liver functional tests indicate some hepatic insufficiency;

11. during an allergic paroxysm, there is an increase in the concentration of the blood, the refractive index is lowered, there is a drop in the pH and the alkali reserve falls, and the blood pressure is lowered; but the most characteristic feature of the blood in allergy is an eosinophilia, usually about five per cent.

Food Allergy.

It is particularly in children that foods may give rise to allergic symptoms, the commonest being milk, eggs and wheat. Although positive skin reactions to foods are not uncommonly found, it is only rarely that a definite relationship can be demonstrated in adults between the food and the production of symptoms.

Allergy which is manifested solely or even chiefly by gastro-intestinal symptoms is stated to be very unusual. This may, however, be due to its non-recognition. Very acute abdominal symptoms, resembling shock, have been described; the important diagnostic feature in such a case is an associated urticaria, which unfortunately

is not always present. Milder and chronic and recurrent forms of food allergy seem to occur, in which abdominal pain and diarrhoea are the most obvious symptoms.

The mechanism of these abdominal symptoms is not clear. Local areas of oedema in the bowel wall confirm the supposition that wheals occur internally. The permeability of the intestinal capillaries may also be a factor. X-ray appearances suggest a spasm in some part of the bowel.

Abdominal symptoms thus described are very common in childhood. Disinclination for certain foods in children may be a protective mechanism.

Food sensitivity may also be caused by the handling of food.

It is uncommon to encounter a case of food allergy that did not begin in the first decade. It is claimed that the therapeutic use of hydrochloric acid may overcome the hypersensitiveness in infants.

Encouraging results have been obtained in asthmatic children by altering the ketogenic-antiketogenic ratio of the diet. Elimination diets are also of value.

Food allergy certainly exists as a definite entity.

Hereditary Predisposition and Idiosyncracy.

The majority of allergic individuals have one or more antecedents with some type of allergic manifestations, and a certain proportion of their children will develop symptoms. Other children, though they may not show symptoms themselves, are capable of transmitting the tendency to allergic phenomena to their offsprings. So that two modes of inheritance appear to be involved:-

(a) germinal or true Mendelian through the germ plasm of the parents, and

(b) placental or serum sensitisation, which is not truly hereditary, being an active or passive sensitisation of the foetus in utero.

There is no definite proof as to what is inherited, but recent work would suggest that a particular biochemical factor is involved.

A comparison of the influence of the hereditary factor in anaphylaxis in animals and allergy in man is instructive in that it appears quite the opposite in the two. Germinal transmission has not been reported in animals but is frequent in man; active sensitisation in utero is difficult in animals, but possible in man;

passive sensitisation is the common mode in animals, but rare in man.

The greater or more complete the hereditary influences the earlier the age at which symptoms will have their onset. Puberty is probably the most important age in allergic individuals. Inheritance also determines the total incidence of hypersensitiveness in that the more complete it is the greater the number of manifestations.

Types of Asthma.

As age advances so the type of asthma changes in detail. In the child, symptoms of general intoxication predominate; the recovery from an attack is more lasting; and predisposing factors are almost invariably dietetic and emotional. In the adult, the outstanding characteristic is the paroxysmal dyspnoea; climatic conditions and fatigue play an important role in causation; and the persistence of symptoms is marked.

In childhood, it is convenient to recognise types as follows:-

1. the normal looking child subject to asthmatic attacks - one third of patients;

2. the typical asthmatic child - two thirds of patients.

In adults, similarly, the following types occur:-

1. normal adults with clear cut attacks separated by considerable intervals - ten per cent. of patients;
2. normal appearing adults with more frequent attacks, but who are still free of symptoms between them - seventy per cent. of patients;
3. asthmatic adults with essentially constant symptoms but without chronic bronchitis and emphysema - ten per cent. of patients;
4. asthmatic adults with chronic bronchitis and emphysema - ten per cent. of patients;

Such a classification, based on clinical findings, is simple and very convenient.

Asthma and X-rays.

X-rays are a useful aid to diagnosis, and have also been employed in treatment.

In a large percentage of patients, X-rays will show nothing abnormal. Characteristic features are the flatness of the diaphragm, its

relative immobility, and the fixation of the chest in the expanded phase. Pulmonary fibrosis is not infrequently observed. And in patients with emphysema the chest appears "blown up".

X-rays are also, of course, of great value in outlining the details of structure of the thoracic organs and any abnormalities associated with them.

In children, especially, they are particularly useful in excluding the presence of a foreign body in the chest.

The treatment of asthma with X-rays is a recent development. It is applied to the chest and spleen, and to other regions at times. The main therapeutic effects are produced on the lymph nodes and the white blood corpuscles. As a method of treatment, it has not as yet substantiated itself.

The Treatment of Asthma.

This resolves itself into the treatment of the acute attack, and the intensive treatment of the asthmatic sufferer to prevent further attacks.

The primary essential of the former is the therapeutic use of adrenaline. In the milder type of attack, this may not, however, be necessary. In such a case, the inhalation of a few drops of

amyl nitrite may be sufficient. In due course, each asthmatic patient discovers a most efficient and ready way of relieving his attacks. It is also important to bear in mind other important details which help to relieve the patient of his discomfort. These are the provision of adequate warmth, the maintenance of rest and quietude and the attention to dietetic details, including the use of stimulants and aperients when necessary.

The solution of adrenaline used should be clear and not in any way discoloured. Unnecessarily large doses are only too frequently employed, and may lead to disagreeable symptoms which should be borne in mind. The correct average dose is 0.25 c.c. of the 1:1000 solution. The older the patient the larger the required dose. In children, it should be used with great care. Tolerance is rarely attained by its use.

Ephedrine has recently been introduced as a substitute for adrenaline. This it is not. Unlike adrenaline, it has definite contra-indications. Its use should be limited to prophylaxis; and its use is more effective in patients in whom there are no bronchial complications.

Other drugs have been from time to time employed to relieve the asthmatic paroxysm. Whatever is used, it is essential to realise that the stopping of an acute attack is of great value in enabling the patient to maintain his general health, a factor which is of paramount importance in all asthmatic patients.

The intensive treatment of the asthmatic sufferer in between attacks begins with an accurate diagnosis. Every effort should therefore be made to elicit the presence or absence of hypersensitiveness to some dust or food, of a focus of infection, of bronchial complications, and so on. It will be found, however, that there are many patients in whom no precise causal agent can be identified.

Treatment must be considered under the following:-

drugs, endocrine and organic extracts,

desensitisation, vaccines and tuberculin,

physical therapy, surgery.

Drugs.

Many drugs are used in this disease for the relief of symptoms and the improvement of the general health. Of these, potassium iodide is

outstanding in its results; and it is often employed in combination with arsenic with excellent results. The use of salicylates, including aspirin, has an interesting theory to support it.

The use of glucose, advocated on biochemical findings, leads to improvement in the general health; it is of greatest value in early life.

Endocrine and organic extracts.

Endocrine therapy is indicated in a limited number of patients, in whom some endocrine dysfunction is obviously present.

Auto-haemo-therapy has been employed in patients under the care of the author with encouraging results. It has a definite place in the therapeutics of uncomplicated allergic asthma. Where complications exist, such therapy depends for any success achieved in the allergic condition on the successful management of the complications. Autogenous serum and defibrinated blood, and blood transfusions, have also been tried with varying results.

Biochemical investigations have also led to the use of liver extracts in this disease. Best results are obtained in the clear-cut

allergic asthmatics, with an initial high red cell count. The improvement in the general condition is often very marked.

Desensitisation.

This never leads to the dramatic results obtained when some specific causative allergen can be avoided or removed. Its use should thus be reserved for those patients in whom such specific causes cannot be avoided or removed entirely.

Specific desensitisation is most commonly carried out by the subcutaneous route, by the "rush" method, or by the weekly method. When the allergen is a common food, the ingestion of gradually increasing doses is recommended. Otherwise in food sensitivities, denaturisation may be employed. Repeated cutaneous reactions may also at times lead to desensitisation.

The use of non-specific protein therapy in asthma is justified by the relief of symptoms often obtained by vaccine treatment, and by the relief of allergic symptoms which accompanies acute infections. It is said that this form of treatment results in the stimulation of the cells of the organism and in an increase in body metabolism.

Peptone and milk are the two substances most commonly employed.

Desensitisation with proteose from the urine is as yet in the experimental stage. In theory, it has much to commend it. The size of the initial dose depends upon the dilution with which a positive intradermal skin reaction is obtained. A severe attack of asthma is claimed to have followed an overdose.

Vaccines and Tuberculin.

Vaccines may produce their effects by the inducing of a specific immunity, directed towards the particular organism used in the vaccine, or by virtue of the non-specific local delayed reaction which may follow their use, or by both these factors. The production of a definite local reaction may indeed be taken as an indication that such vaccine will do good. Autogenous vaccines are most frequently used; but many observers claim equally good results with the stock or non-specific type. If this is so, it is obvious that the question of the hypothetical "third substance" is implicated. On the other hand, recent investigations disclose the interesting fact that bacilli of the Friedlander group

are histamine producers, and these organisms are not infrequently found in the sputa of asthmatics. Vaccines are given in weekly injections, the size of the dose being regulated according to the production of the local reaction. If the vaccine is likely to result in any pronounced improvement, such will generally be observed to occur after the first few doses; and unnecessary prolongation of the treatment is uncalled for; there are, however, exceptions to this statement. Whereas it is uncommon for general systemic reactions to follow ordinary subcutaneous doses, it must be borne in mind that serious accidents have been reported; and there are certain definite contra-indications to their use. Generally speaking, it cannot be said that they have proved of any permanent therapeutic value.

In tuberculin therapy, the production of local reactions following the subcutaneous doses seems to be just as important. In fact, any improvement does not appear to be in any way different from that effected by most ordinary vaccines. Active tuberculosis is, of course, a definite contra-indication.

Physical Therapy.

Actino-therapy does not affect asthma directly;

in a few patients it may have a slight sedative and tonic action.

Bronchoscopy is used to remove excessive and tenacious bronchial secretions, and for the direct application of drugs to the bronchial mucous membrane. It is thus in cases with a chronic infection of the trachea and bronchi that it has its greatest sphere of usefulness. By its means, swabs from such an infected source may also be obtained. Clinical improvement is undoubtedly observed after the treatment described; it is, however, only temporary.

The intra-tracheal injection of heavy oils through the crico-thyroid membrane is also being tried.

Surgery.

The establishment of operations for the treatment of angina pectoris has led to similar operations being attempted for the relief of asthma. Anatomical considerations demonstrate how intricate and delicate must such operations be to be successful. At any rate, such as have been done on the sympathetic and vagus can be regarded as of no value in the treatment of asthma.

The para-vertebral injection of the dorsal ganglia is apparently a safe procedure, which

may yet prove of value.

Surgery of the naso-pharynx and sinuses should be undertaken only as a part of a definite therapeutic programme. In the absence of obvious pathology and definite deformities, antiseptic treatment and drainage is the method of choice.

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Conclusions.

1. Asthma as a disease has been recognised from earliest times, and the development of our present knowledge has been a gradual process.
2. Asthma represents the lung manifestations of a group of diseases, which have as a common fundamental basis the phenomena of hypersensitiveness.
3. The phenomena of hypersensitiveness is exhibited in man as Allergy and in laboratory animals as Anaphylaxis, and is taken to include all reactions in which a hypersusceptibility to some foreign agent is evidenced as compared with normal.
4. The chemical problems of experimental anaphylaxis and human hypersensitiveness are very similar.
5. A similarity in pathology exists also between these two conditions.
6. The mode of sensitisation varies somewhat in anaphylaxis and allergy; but the resulting condition of hypersensitiveness is essentially the same.
7. Failure to find that desensitisation has occurred after recovery from a general

reaction in a hypersensitive patient makes it difficult to see how desensitisation in any ordinary sense takes place in human allergy.

8. There is substantial evidence to uphold the view that asthma is a manifestation of a condition like anaphylaxis in a sensitive subject.

9. This state of allergy is not just merely a state of altered reactivity to various substances; for there are important modifying or predisposing factors.

10. The allergic individual can be shown to possess certain very definite characteristics.

11. The bronchial obstruction in asthma is due to a spasm of the bronchial musculature.

12. In allergy, a very important role is probably played by the vagus.

13. The clinical lesions found in the naso-pharynx are merely a part of the fundamental pathological changes which occur in asthma.

14. There is biochemical evidence to support the theory of toxaemia in etiology.

15. The ingestion of wholesome and normally well tolerated foods may give rise to allergic symptoms, especially in children, and simulate a surgical emergency.

16. Tuberculosis merely predisposes to asthma in the same way as any other respiratory infection by virtue of the tissue damage produced.

17. A decrease in the normal secretion of adrenalin, with a disturbance of the vago-sympathetic balance, may explain the influence of the nervous factor in asthma.

18. Nearly all asthmatics lose their symptoms at a height of 4,000 feet, and the bio-chemistry of the blood is probably respon-sible.

19. The neglect of asthma in children is followed by the presence in the community of a number of individuals, incapable of earning their own living.

20. The benefits derived from spa treatment are due to the routine, psychology and free carbon dioxide vapours.

21. The end products of protein digestion are the amino-acids, which go to form essential secretions and enzymes.

22. The union of antigen and antibody in anaphylaxis and allergy seems to injure the tissues and liberate a histamine-like substance which gives rise to symptoms.

23. The state of allergy is characterised by a diminished existence to histamine-like substances.

24. In the intestines, bacteria attack protein decomposition products, and amines (including histamine) and other bodies are formed.

25. Protein skin reactions are used to demonstrate that an allergic patient reacts to some foreign substance in a way different from normal individuals, and are of value in demonstrating the activity of a known specific allergen.

26. Relief of symptoms following removal of a suspected allergen in the instance of a positive reaction is definite proof of the value of such a reaction.

27. The asthmatic individual is characterised by a definite biochemical make-up.

28. The specific allergen concerned in asthma is secreted in the urine during the attack.

29. It is unusual to find in adults that a positive skin reaction for foods necessarily implicates such foods as causal agents in the allergic attack.

30. The same manifestations which result from the entry from without of foreign protein substances into the body can be produced by causes, such as bacteria, within the body.

31. Bacterial allergy differs, however, from ordinary allergy in the behaviour of the skin test, and in the fact that treatment with vaccines very rarely produces general reactions.

32. The transmission of the allergic diathesis cannot be explained solely according to Mendelian laws, as two modes of inheritance appear to be involved.

33. The influence of the hereditary factor appears to be quite different in animal anaphylaxis and human allergy.

34. Asthma changes in type with the advance of age, intoxication predominating in childhood and respiratory symptoms in adults.

35. Classifications of asthma based on etiology and pathology are unsatisfactory; and it is convenient to use one based on clinical findings.

36. X-rays are a useful adjunct to diagnosis in asthmatic patients.

37. The treatment of the acute asthmatic paroxysm centres around the correct use of adrenaline.

38. To enable an asthmatic patient to maintain his general health, every effort should be made to abort or cut short the acute paroxysms.

39. The discovery of the fundamental cause is the essence of the intensive treatment of the asthmatic sufferer in between attacks.

40. The general health of the patient can be very much improved by the use of Glucose, and liver extracts.

41. Auto-haemo-therapy is of decided value in the treatment of uncomplicated allergic asthma.

42. Specific desensitisation is disappointing, generally, and should be reserved for those patients in whom specific causes cannot be removed or avoided entirely.

43. Vaccines cannot be said to have proved of any permanent therapeutic value.

44. Bronchoscopy is of value in the treatment of gross bronchial complications, but the sphere of its use is limited.

45. Surgery cannot be said at present to have any part in the treatment of asthma, except in the presence of obvious pathology of the naso-pharynx.

46. The asthmatic can always be helped in one way or another and his general health improved.

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